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BIBLIOGRAPHIC DATA SHEET	1. Report No. 0-309-02314-9	2.	3. Recipient's Accession No. PB245123

4. Title and Subtitle

Nickel

5. Report Date 3/75

6.

7. Author(s) Committee on Medical and Biologic Effects of Environmental Pollutants, National Research Council

8. Performing Organization Rept. No.

9. Performing Organization Name and Address
National Academy of Sciences
2101 Constitution Ave
Washington, DC 20418

10. Project/Task/Work Unit No.

11. Contract/Grant No.
68-02-0542

12. Sponsoring Organization Name and Address
Environmental Protection Agency
401 M St. SW
Washington DC

13. Type of Report & Period Covered

14.

15. Supplementary Notes part of Series on Medical and Biologic Effects of Environmental Pollutants

16. Abstracts

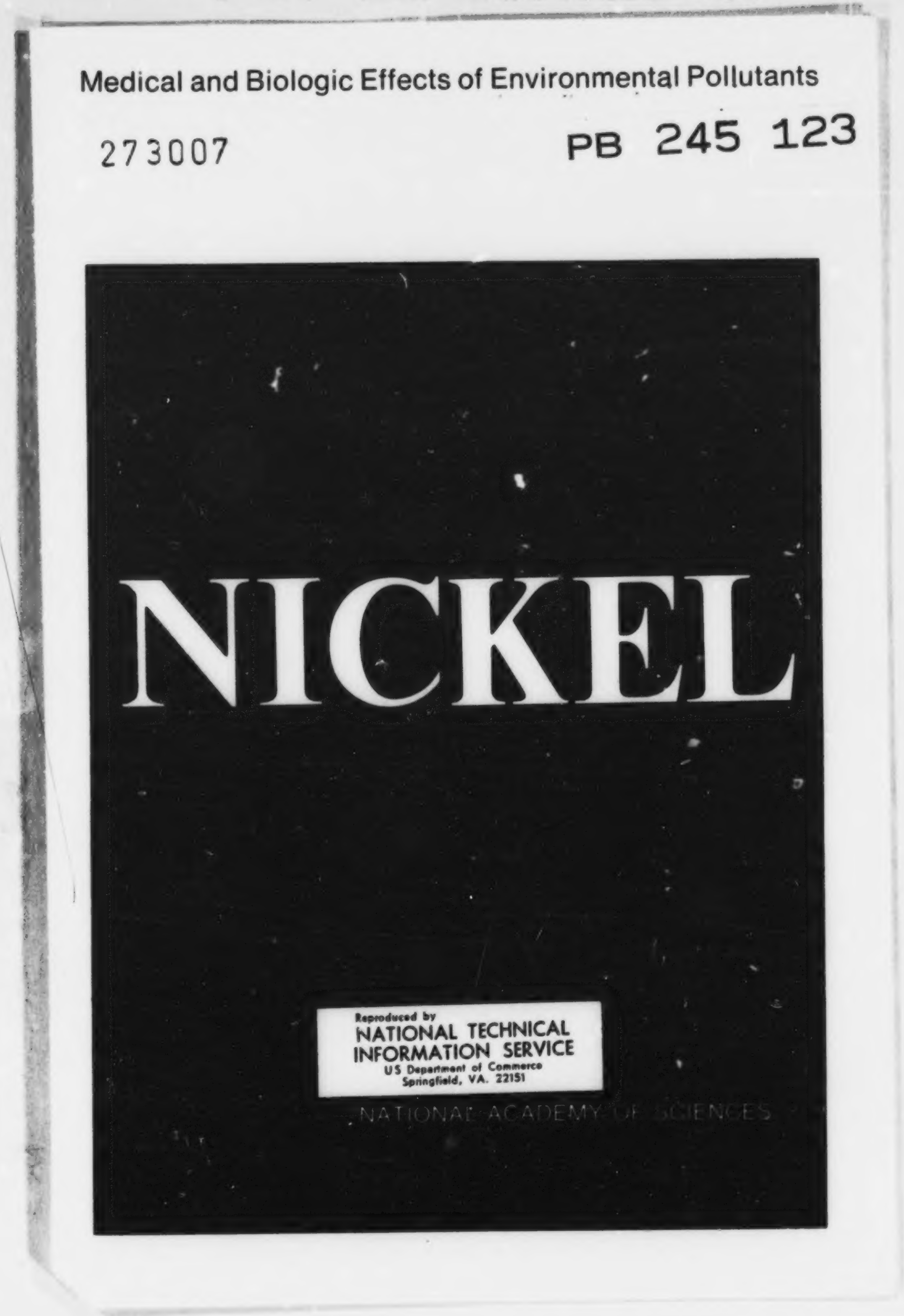
Assembles, organizes, and interprets all available information on nickel and its compounds, presenting a balanced and comprehensive survey of its relation to health. Describes the natural sources of nickel and the production of nickel from its ores; its physical and chemical nature; its measurement; its relation to other pollutants; the manufacturing processes that use nickel; the recycling of nickel in the biosphere; occupational hazards from nickel; and community exposures and margins of safety. Information is also presented on experimental studies related to the metabolism, toxicity, carcinogenicity, and mutagenicity of nickel and its compounds. Recommendations for monitoring and controlling nickel in the environment are presented.

17. Key Words and Document Analysis. 17a. Descriptors

17b. Identifiers/Open-Ended Terms

17c. COSATI Field/Group

18. Availability Statement paperbound volume available from Printing and Publishing Office, National Academy of Sciences, 2101 Constitution Ave, Washington DC for $10.75. Microfiche available from NTIS.	19. Security Class (This Report) UNCLASSIFIED	21. No. of Pages 234
	20. Security Class (This Page) UNCLASSIFIED	22. Price $8.75



Medical and Biologic Effects of Environmental Pollutants

273007

PB 245 123

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Medical and Biologic Effects of Environmental Pollutants

NICKEL

Committee on
Medical and Biologic Effects of
Environmental Pollutants

DIVISION OF MEDICAL SCIENCES
NATIONAL RESEARCH COUNCIL

NATIONAL ACADEMY
OF SCIENCES
WASHINGTON, D.C. 1975

1a

Other volumes in the Medical and Biologic Effects of Environmental Pollutants series (formerly named Biologic Effects of Atmospheric Pollutants):

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, acting in behalf of the National Academy of Sciences. Such approval reflects the Board's judgment that the project is of national importance and appropriate with respect to both the purposes and resources of the National Research Council.

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The work on which this publication is based was performed pursuant to Contract No. 68-02-0542 with the Environmental Protection Agency.

Library of Congress Cataloging in Publication Data

National Research Council. Committee on Medical and Biologic Effects of Environmental Pollutants. Nickel.

(Medical and biologic effects of environmental pollutants)
Bibliography: p.
Includes index.
1. Nickel–Toxicology. 2. Nickel–Environmental aspects. I. Title. [DNLM: 1. Nickel. 2. Nickel–Poisoning. QV290 N279n]
RA1231.N44N37 1975 615.9'25'625 75-1475

ISBN 0-309-02314-9

Available from
Printing and Publishing Office, National Academy of Sciences, 2101 Constitution Avenue, Washington, D.C. 20418

Printed in the United States of America

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Acknowledgments

This document was written by the Panel on Nickel under the chairmanship of Dr. F. William Sunderman, Jr. Although each section was prepared initially by a member of the Panel or an invited contributor, some material was later combined, and the total document was reviewed and approved by the entire Panel and thus represents its cooperative effort. Dr. Sunderman was responsible for the introduction, large parts of the sections on nickel metabolism in man and animals and on nickel toxicity, and much of the sections on nickel carcinogenesis and nickel in the reproductive system; he also wrote the part of Appendix B that deals with the analysis of nickel in biologic material.

Dr. John A. Fellows and Mr. Horace T. Reno were jointly responsible for the chapter on sources and prevalence of nickel in the environment, in which is included material supplied by Dr. Samuel I. Shibko of the Food and Drug Administration. The sections on binding to biologic substances and effects on enzymatic activities, in the chapter on nickel metabolism in man and animals, were prepared by Dr. Gunther L. Eichhorn. In the same chapter, Dr. Brian A. Curtis wrote the section on nickel and excitable tissues. Dr. Frederick Coulston contributed material on nickel toxicity and on teratogenesis and mutagenesis of nickel.

Dr. M. H. Samitz was solely responsible for the chapter on dermatologic aspects of nickel. Dr. Ernest Mastromatteo was partly responsible,

with Dr. Sunderman, for the section on epidemiology in the chapter on nickel carcinogenesis and also made use of material contributed by Dr. Joan C. McEwan of the Ontario Department of Health. Dr. Philip W. West prepared the section on analysis of nickel that appears in Appendix B, except the part on analysis in biologic material. A portion of the section that deals with methods was taken directly from *Health Laboratory Science*, with the permission of that journal. The data appearing in Appendix A were provided by the Environmental Protection Agency (EPA).

Comments made by members of the Committee on Medical and Biologic Effects of Environmental Pollutants during the in-depth presentation of the draft nickel report were of assistance in developing the document. The Panel is especially indebted to Dr. Gordon J. Stopps, who served as Associate Editor, and to those anonymous reviewers whose services he enlisted to carefully review and constructively criticize the work.

The Panel is indebted to the Editor of the Division of Medical Sciences, Mr. Norman Grossblatt, for the effective contribution he made by his capable editing of the document. Valuable assistance to the Panel in its deliberations was given by Dr. Robert J. M. Horton of the EPA; Dr. Kenneth Bridbord served as liaison representative from that agency. In locating and verifying references and in obtaining information for the Panel, much use was made of the valuable resources of the National Research Council's Advisory Center on Toxicology, the National Academy of Sciences Library, the National Library of Medicine, the National Agricultural Library, the Library of Congress, and the Air Pollution Technical Information Center. Acknowledgment is also made of the assistance received from the Environmental Studies Board, National Academy of Sciences–National Academy of Engineering, and divisions of the National Research Council.

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1

Introduction

PURPOSE

This is a report of a study of the biologic effects of nickel. In conducting the study, the Panel on Nickel assembled, organized, and interpreted all available information on nickel and its compounds and drew conclusions regarding the effects of these on humans and other animals.

The objective of this document is to present a balanced and comprehensive survey of nickel in relation to health for the information of the scientific community and the general public and for the guidance of standard-setting and regulatory agencies. The report describes the sources of nickel, its physical and chemical nature, its measurement, its relation to other pollutants, its biologic effects and margins of safety, and dose-response relations (if known) and offers recommendations for monitoring and controlling nickel in the environment and for further research.

The statements contained in the document are supported by references to the scientific literature whenever possible or are based on a consensus of the members of the Panel.

HISTORICAL NOTE

In 1826, C. G. Gmelin,[201] professor of chemistry at the University of Tübingen, reported the first investigation of the biologic effects of nickel. Gmelin's findings are summarized in Table 1-1, with the results of later studies of the toxicity of nickel salts in experimental animals that were published in the 1880's. The latter investigations, performed by Richet,[496] Stuart,[577,578] Coppola,[95,96] Testa,[637] Hare,[220] and Laborde and Riche,[321] were stimulated by clinical interest in the therapeutic use of nickel bromide as an antiepileptic drug and of nickel sulfate in severe diarrhea. Interest in nickel toxicity may also have been stimulated by an apparent rumor that Emperor Franz Josef of Austria had developed an illness due to the use of nickel cooking pots.[313] Table 1-2 summarizes the therapeutic uses of nickel salts during the years 1853–1885. These clinical reports retain scientific value, as well as historical interest, because they represent the only documentation of the pharmacologic effects of these salts in man.

Therapeutic use of nickel sulfate and nickel bromide was gradually abandoned after extensive animal studies of the acute and chronic toxicity of nickel salts by Dzergowsky *et al.*[133] in 1906–1907 and by Lehmann[333] in 1908–1909. The discovery of nickel carbonyl by Mond *et al.*[414] quickly led to recognition of the extraordinary toxicity of this volatile liquid,[388] and numerous studies of the acute toxicity of nickel carbonyl in man and animals were reported from 1891 to 1908, as summarized in Chapter 4. In 1912, Herxheimer[241] published the classic description of nickel dermatitis in industrial workers.

TABLE 1-1 Studies of Toxicity of Nickel Compounds in Experimental Animals

Authors	Date	Investigations and Observations
Gmelin[201]	1826	Administration of nickel sulfate to rabbits and dogs by stomach tube produced severe gastritis and fatal convulsions; sublethal dosage of nickel sulfate in dogs produced cachexia and conjunctivitis
Richet[496]	1881	Fish could survive for 1 day in water that contained nickel chloride in nickel concentrations of 0.125 g/liter
Stuart[577,578]	1883–1884	Established acute lethal dosages of nickel oxide by subcutaneous injections in frogs, pigeons, guinea pigs, rats, rabbits, cats, and dogs; concluded that acute nickel toxicity affects primarily the vascular, alimentary, and nervous systems
Coppola[95,96]	1885–1886	Established acute lethal dosages of nickel chloride by parenteral routes in frogs, guinea pigs, rabbits, and dogs
Testa[637]	1886	Studied the direct effects of nickel bromide on cerebral excitation
Hare[220]	1886	Studied effects of nickel bromide on sciatic reflexes in frogs and on pulse and blood pressure in dogs
Laborde and Riche[321]	1888	Established acute lethal dosages of nickel sulfate in guinea pigs, rabbits, and dogs

TABLE 1-2 Use of Nickel Salts as Therapeutic and Antiseptic Agents

Authors	Date	Observations
Simpson[549]	1853	Administered nickel sulfate orally as a "metallic tonic" and found benefit in a patient with recurrent headache, chlorosis, and amenorrhea
Palmer[459]	1868	Administered nickel sulfate orally to a patient with facial neuralgia and found analgesia and sedation
Shulz[545]	1882	Reported that nickel chloride was superior to mercuric chloride as a bacterial antiseptic, because it was less toxic in animals and its green color led to ready recognition
DaCosta[109]	1883	Administered nickel chloride, sulfate, acetate, phosphate, and bromide to patients; observed that sulfate produced "excellent results . . . in doses from one to two grains four times daily, in cases of obstinate diarrhea" and that bromide in oral dosage of 5 grains three times daily was an effective sedative and antiepileptic drug
Leaman[329]	1885	Administered nickel bromide to 50 epileptics and found it superior to other bromides as an antiepileptic drug; it was also beneficial in relief of headache

Bertrand and Macheboeuf[46] in 1925 were the first investigators to observe the presence of traces of nickel in tissues from man and several animals, and they also discovered the relative richness of nickel in marine mollusks. In 1936, Bertrand and Nakamura,[48] on the basis of nutritional experiments that appear in retrospect to be unconvincing, first suggested that nickel might play a normal physiologic role.

The following references are of particular value: Mond,[413] for the history of the discovery of nickel carbonyl; Amor[9] and Trout,[653] for the history of early industrial exposures to nickel carbonyl; Peller[472] and Hueper,[261] for information on the recognition of the carcinogenic hazards in nickel refineries; and Howard-White,[255] Boldt,[53] and Thompson and Beasley,[639] for the history of nickel technology.

2

Sources and Prevalence of Nickel in the Environment

Nickel is a silvery metal with a specific gravity of 8.9, a melting point of 1,455 C, and a boiling point of about 2,900 C. It is insoluble in hot and cold water, soluble in dilute nitric acid, slightly soluble in hydrochloric acid and sulfuric acid, and insoluble in ammonium hydroxide. Its atomic weight is 58.71. It is a composite of five stable isotopes: nickel-58, -60, -61, -62, and -64; measured by relative abundance, these constitute 67.88%, 26.23%, 1.19%, 3.66%, and 1.08%, respectively, of the whole. Seven unstable isotopes and their half-lives have been identified: nickel-56, 6 days; nickel-57, 36 h; nickel-59, 8 × 10^4 yr; nickel-63, 92 yr; nickel-65, 2.5 h; nickel-66, 55 h; and nickel-67, 50 s. Nickel normally occurs in the 0 and 2+ valence states, but it can also exist in valence states of 1−, 1+, 3+, and 4+. Nickel is ubiquitous in the earth and its waters, but probably not in the atmosphere.

OCCURRENCE OF NICKEL IN THE EARTH'S CRUST AND WATERS

Rocks and Soils

Nickel constitutes about 0.008% of the earth's crust. By far the largest part is in igneous rocks, of which nickel constitutes approximately 0.01%. The earth's core contains 8.5% nickel; meteorites have been found to contain 5–50% nickel. Nodules that are rich in nickel have been discovered on the ocean floor.

Rocks that form the geologic units of the upper part of the earth's crust supply most of the material from which soils are formed and from which all waters derive their inorganic constituents. Therefore, the composition of the soils depends on the composition of the rocks.

Pettijohn[478] has estimated that about 75% of the earth's surface is underlaid with sedimentary rocks and 25% with igneous rocks. Among the igneous rocks in the lithosphere, ultramafic (or ultrabasic—i.e., containing iron and magnesium and little or no silica) rocks are the principal sources of nickel, ranging in content from 0.016% in basalt and gabbro to an average of 0.20% in peridotite. Diorite contains 0.004% nickel, and the silicic (acid) granitic rocks contain only 0.0002%. Among the major sedimentary rocks, shale and carbonate rocks contain an average of 0.005% nickel; and sandstone, with a high percentage of silica, contains only 0.0001%. Cobalt usually occurs with nickel, ranging from a trace to as much as 1 part cobalt to 10 parts nickel.

A study by Turekian and Wedepohl[656a] in 1961 showed an inverse relation between the nickel in sedimentary and igneous rocks and the silica content. As shown in Figure 2-1, with the exception of carbonates, rocks low in silica are high in nickel, and those high in silica are relatively low in nickel. Farm soils of the world contain nickel at 0.0003–0.1%. The average farm soil in the United States contains nickel at more than 0.003%. Soils with less than 0.0003% are too acidic to support normal plant growth.

In view of the widespread occurrence of nickel in the lithosphere and the sharp variations in the nickel content of soils from one area to another, surface and subsurface sampling to demonstrate contamination from outside sources must be interpreted with caution. Researchers at the University of Toronto, in Canada, have studied nickel in the soil, plants, and waters around the Sudbury smelters and nickel concentration in relation to distance from highway and traffic density (personal communication). Their work has shown contamination of the soils, vegetation, and waters around the smelter. They concluded that in the Sudbury region the presence of nickel is related more to industrialization than to highway traffic. Studies of nickel pollution on a farm near a nickel refinery at Clydach, in South Wales, England, in 1934–1936 and in 1971 have been reported by Ashton.[17] Sampling of vegetation indicated a marked decrease in nickel contamination since the 1930's. The decrease was attributed to a cleaner process of nickel extraction at Clydach. Soil on the farm was not sampled in the 1930's. In 1971, the nickel content of sampled topsoil ranged from 0.02 to 0.35%.

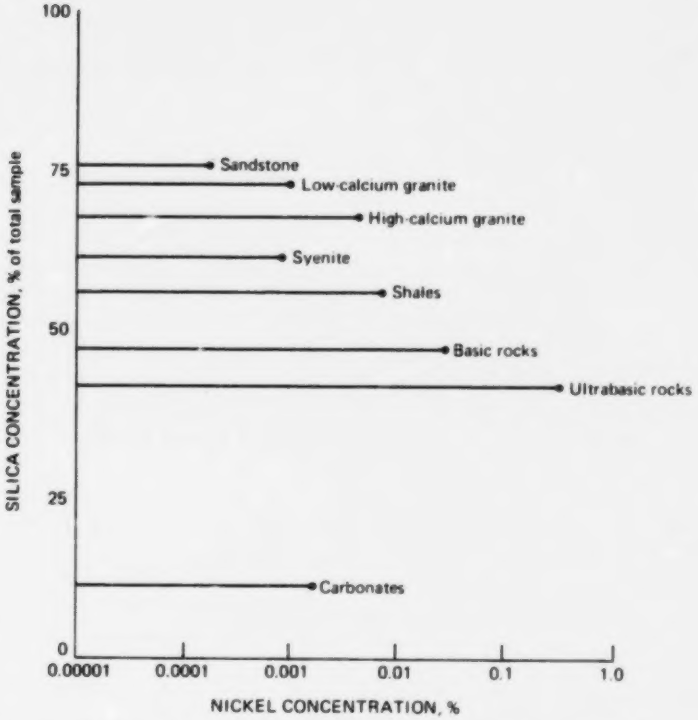

FIGURE 2-1 Average nickel content in various sedimentary and igneous rocks.

Ore Deposits

Nickel ore deposits are formed by magmatic segregation of the ultramafic rocks in which nickel is concentrated in veins, stringers, or fissure fillings in the surrounding host rock. Pentlandite [$(FeNi)_9S_8$], chalcopyrite ($CuFeS_2$), and pyrrhotite (Fe_xS_{x+1}) are sulfide minerals commonly found in nickel ore deposits.

Other nickel ore deposits are in lateritic material formed by the weathering of ultramafic ferromagnesium silicate rocks. In these deposits, parts of the silica, iron, and magnesium have been leached by groundwaters, leaving a nickel-enriched residue. Part of the nickel is mixed with other elements in unidentifiable mineral forms, but some of it occurs in the mineral garnierite, a hydrous nickel magnesium silicate that has been described as a variety of chrysotile serpentine in which nickel has replaced part of the magnesium. This latter mode of occurrence is significant because the principal asbestos mineral is chrysotile in its naturally occurring fibrous form. However, there are several controversies in recent literature dealing with nickel occurrence in serpentines. Bureau of Mines petrographers (personal communication) conclude that "most authors indicate that silicate is the primary source of Ni in the rocks they are studying. However, many of these authors have not made a detailed study and seem to be inferring Ni origin from the work and/or written word of previous authors." Nevertheless, a few researchers have actually detected nickel substituted for magnesium in silicates.

Coal

Silicon, aluminum, iron, calcium, magnesium, sodium, potassium, and sulfur constitute the main part of the mineral matter of most coal. Nickel, with 21 other trace elements, occurs in virtually all coal, but in very minor quantities. The nickel content of coal can be determined by spectrochemical analysis of the ash after the coal has been burned. Such analyses do not include any nickel that is vaporized as nickel carbonyl. Bureau of Mines studies[1] have shown that nickel content varies significantly according to geographic origin of North American coal and that western coals contain less nickel than eastern and midwestern coal. In 600 analyses of coal taken from eight eastern states, the average ash content of the coal was 9.3%, and the average nickel content of the ash was 0.0209%. Those figures may be compared with an average ash content of 10.5% containing 0.0262% nickel in 123 analyses of coal from seven midwestern states and an average ash content of 9.8% containing only 0.0054% nickel in 104 analyses of coal from eight western states. Thus, the average nickel content of U.S. coal is about 0.06 lb/ton in the midwestern states, 0.04 lb/ton in the eastern states, and 0.01 lb/ton in the western states. If these quantities are related to total estimated remaining coal resources in the several geographic areas, the nickel content of U.S. coal resources might total as much as 28 million tons. Such a figure is completely speculative, however, in view of the wide variation in nickel content of coal.

The Bureau of Mines studies also indicate that the average nickel content of the ash of coal from western states is usually less than that of the earth's crust. Therefore, this coal cannot be considered as a potential source of nickel supply. However, coal of the eastern and midwestern states contains substantially more nickel than the average of the earth's crust and might be considered as a nickel source. The total nickel supply from U.S. coal resources might be as much as 12 million tons. Any recovery from coal would necessarily be from coal ash because of the low nickel concentrations (0.8–1.2 lb/20 tons of coal), and supply would vary with the demand for coal. At the current coal demand, an estimated 13,000 tons of nickel might be contained in the ash of coal burned in the eastern and midwestern states in 1970. Only the ash from coal burned at utility plants might be considered generally available for nickel recovery, however. The quantity of nickel that might be available from the processing of coal ash is estimated at about 8 million tons, if all the ash currently available from utility plants were processed for nickel recovery.

Petroleum

The nickel content of domestic crude oil reportedly ranges from 0.00014 to 0.0064% (median, 0.00043%; average, 0.00142%) and that of imported crude oil, from 0.000003 to 0.00295% (median, 0.0006%; average, 0.0010%).[5]

Bureau of Mines researchers determined selected properties of 186 samples of crude oil from important fields throughout the world to augment the bureau's data bank on crude-oil properties and to provide a basis for identifying the source of oil spilled or dumped on commercial waterways. These data have been published.[6] (It is worthy of note, anticipating discussion later of nickel emission to the atmosphere from combustion of petroleum products, that nickel:vanadium ratios afford in some cases a means of identifying the source of fuel oil burned by any plant from the nickel:vanadium ratio in its effluent.)

The nickel content of typical commercial residual fuel oil reported in the *Petroleum Products Handbook*[477] ranges from nil to 0.00002%. Complete analyses of stack gases, fly ash, and residual material at power-generating plants are not available.

Water

The nickel content of seawater ranges from 0.1 to 0.5 μg/liter. In most groundwaters, nickel has not been identified; and in instances where it has been detected, analysts theorize that it is probably in colloidal form.[658]

It has been determined that, in the rock-weathering process, nickel goes into the insoluble minerals of the hydrolysates. Therefore, any nickel in surface or groundwaters is likely to be in small amounts, unless its presence is due to industrial pollution.[316]

Kopp and Kroner[316] reported that nickel was found in U.S. waters with a frequency of 16% and at an overall mean concentration of 19 μg/liter. The detection limit for nickel in water with total dissolved solids of 400 μg/liter was 20 μg/liter. If the dissolved solids amounted to 200 μg/liter, the detection limit would be 10 μg liter. The major river basins in the United States are shown in Figure 2-2. The mean concentrations of nickel in waters from these basins are listed in Table 2-1.

The Missouri River and Western Gulf basins had the lowest frequency of nickel detection and among the lowest mean concentrations, at 5 and 3 μg/liter, respectively. The highest mean concentration was 130 μg/liter, in the Cuyahoga River at Cleveland, Ohio. Kopp and Kroner's reporting of mean concentration of nickel based only on occurrences must be interpreted in light of the frequency of detection. In a large percentage (average, 84%) of the samples, nickel was not detected; these samples were not used in calculating mean concentrations.

Table 2-2 lists nickel concentrations determined by spectrographic analysis of evaporated residue of selected samples taken in 1962 of public water supplies of the 100 largest cities in the United States, as reported by the Geological Survey.[131] Spectrographic analyses in this study could detect nickel concentrations as low as 0.001% in the residue.

TABLE 2-1 Nickel in Water from Major River Basins of the United States[a]

River Basin	Mean Nickel Concentration, μg/liter[b]	Frequency of Detection, %
Northeast	8	22.0
North Atlantic	8	28.1
Southeast	4	20.9
Tennessee River	4	8.8
Ohio River	31	25.2
Lake Erie	56	53.2
Upper Mississippi	15	15.2
Western Great Lakes	10	9.1
Missouri River	5	2.0
Southwest-Lower Mississippi	17	9.7
Colorado River	12	8.0
Western Gulf	3	2.1
Pacific Northwest	10	10.5
California	10	13.8
Great Basin	4	15.8
Alaska	5	11.1

[a] Derived from Kopp and Kroner.[316]

[b] Only occurrences of nickel were used in calculating the mean.

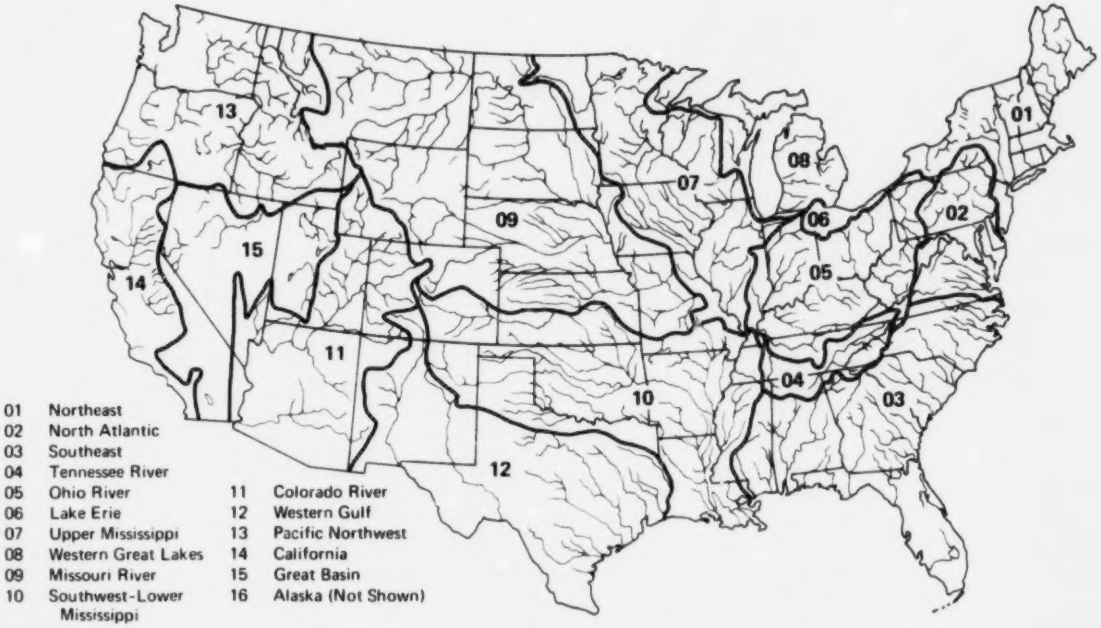

FIGURE 2-2 Major river basins of the United States.[316]

The samples were taken at the water source, in storage, and in various stages of treatment. The data substantiate the findings of Kopp and Kroner and strengthen the conclusion that most of the nickel in surface waters and groundwaters originates from man's activities. Nickel in natural waters apparently would present a health hazard only in most unusual circumstances.

McNeely *et al.*[392] compared nickel concentrations in samples of tap water from the municipal water supplies of Hartford, Connecticut, and Sudbury, Ontario. The mean concentration of nickel in five samples from Hartford was 1.1 μg/liter (standard deviation, ± 0.3 μg/liter; range, 0.8–1.5 μg/liter). In comparison, the mean concentration of nickel in seven samples from Sudbury was 200 μg/liter (standard deviation, ± 43 μg/liter; range, 141-264 μg/liter). Data on the nickel content of surface waters and drinking water of Ontario are summarized in Table 2-3.

On the basis of analyses of nickel concentrations of 969 water supplies in the United States during 1969–1970 (Table 2-4), the average concentration of nickel in water samples taken at the consumer's tap was 4.8 μg/liter. With an estimated daily intake of 2 liters of water, an adult would consume approximately 10 μg of nickel per day in drinking water.

INDUSTRIAL SOURCES OF ENVIRONMENTAL NICKEL

Processing of Nickel

The principal nickel-producing areas of the world are shown in Figure 2-3. Nickel production in 1968–1970 by country is summarized in Table 2-5. All Canadian, Finnish, Rhodesian, and South African nickel and some Russian and Australian nickel are produced from sulfide ores. The remaining nickel represented in Table 2-5 is produced from oxide ores.

Most nickel is used in alloys to make a wide variety of consumer hard goods. The nickel used to make stainless steel reaches practically every household in the United States, either in cooking utensils, in flatware, or in kitchen appliances. Nickel consumption as reported to the Bureau of Mines in 1970 by use is summarized in Table 2-6. Bureau of Mines data indicate that more than 600 companies in the United States are primary users of nickel. Among the approximately 150 users that make alloys, about 55% produce castings and 45% produce forgings. These consumers generally use electric furnaces to melt nickel with other metals in making the alloys.

TABLE 2-2 Nickel Content of Residue of Selected Samples of Public Water Supplies of 100 Largest Cities in the United States, 1962, μg/liter[a]

- Alabama
  - Birmingham <0.4, <1.9, 3.4
  - Mobile 1.1
  - Montgomery ND[b]
- Arizona
  - Phoenix <8, <5.3, ND
  - Tucson ND, <3.5
- California
  - Fresno ND
  - Long Beach 4.0, 9.8
  - Los Angeles 4.8
  - Oakland 1.0
  - Sacramento <1, <2
  - San Diego <7.8
  - San Francisco 3.3, 4.1
  - San Jose ND
- Colorado
  - Denver 0.7, ND, 3.9, 3.2, ND, 5.5
- Connecticut
  - Bridgeport 1.4, 1.3, <0.6
  - Hartford <1.0
  - New Haven 1.9, 0.7
- District of Columbia
  - Washington 7.8, 8.3, 8.5
- Kansas
  - Kansas City 4.5
  - Topeka ND
  - Wichita <3.9
- Kentucky
  - Louisville <2.4, <3.0
- Louisiana
  - Baton Rouge ND, <3.9, <3.3, <3.0
  - New Orleans 2.7, 9.4, <2.5
  - Shreveport 21.0, 2.1, 3.5
- Maryland
  - Baltimore 5.8, 4.0, 4.7
- Massachusetts
  - Boston 1.1
  - Springfield 0.9, 0.7
  - Worcester 0.8
- Michigan
  - Detroit 11.0, 5.6
  - Flint 15.0, 6.1
  - Grand Rapids 6.2, <2.3
- Minnesota
  - Minneapolis 4.4, 2.0, 8.4
  - St. Paul 4.1, 5.3
- Ohio
  - Akron 2.6
  - Cincinnati <2.9
  - Cleveland 6.5
  - Columbus ND, <2.6
  - Dayton 34.0
  - Toledo 3.9
  - Youngstown 3.0
- Oklahoma
  - Oklahoma City 7.6, 25.0
  - Tulsa 9.2, 2.0
- Oregon
  - Portland 0.6
- Pennsylvania
  - Erie 8.4
  - Philadelphia 7.7, 13.0
  - Pittsburgh 3.1, 2.1
- Rhode Island
  - Providence 0.9
- Tennessee
  - Chattanooga <2.2, <2.4
  - Memphis 1.7, <1.2, <1.3, <1.7
  - Nashville 1.6, <1.6

- Florida
  - Jacksonville 4.7, ND
  - Miami ND, 59.0, <4.1, 1.4
  - St. Petersburg <36, ND
  - Tampa 7.0
- Georgia
  - Atlanta 1.2, 0.7
  - Savannah 0.9, 1.1, ND
- Hawaii
  - Honolulu ND, <2.6, <2.6
- Illinois
  - Chicago 3.2, 3.0, 7.4, <2.7
  - Rockford ND
- Indiana
  - Evansville 3.5
  - Fort Wayne 9.6, 2.5
  - Gary 3.4
  - Indianapolis 3.9, <30.0
  - South Bend 9.0, <4.8, 3.2
- Iowa
  - Des Moines <3.0
- Mississippi
  - Jackson 1.1
- Missouri
  - Kansas City 15.0, 3.6
  - St. Louis 4.1, 4.8
- Nebraska
  - Lincoln <4.1
  - Omaha <4.6
- New Jersey
  - Jersey City 2.2
  - Newark 0.9, 1.5
  - Paterson 3.7, 0.9
- New Mexico
  - Albuquerque ND, ND, 3.3
- New York
  - Albany 2.6, 1.4
  - Buffalo 5.1, <2.6
  - New York City 1.6, 2.3, <3.9
  - Rochester <2.5, <1.4
  - Syracuse ND
  - Yonkers <4.1, 6.8, 1.4
- North Carolina
  - Charlotte 0.7, 0.5
  - Greensboro 1.3
- Texas
  - Amarillo ND, ND
  - Austin <2.7, <2.9, 3.3
  - Corpus Christi <4.9
  - Dallas 2.9, <2.8, 5.2
  - El Paso ND, <6.4, <3.7, 6.3, ND, ND
  - Fort Worth 4.3
  - Houston <6.0, ND, ND, 3.3, 4.5
  - Lubbock ND, <5.1, <15.0
  - San Antonio ND
- Utah
  - Salt Lake City 18.0, 11.0, <2.7, 7.2, <5.4, 6.0, 5.7
- Virginia
  - Norfolk 1.9, 2.0
  - Richmond 1.0
- Washington
  - Seattle ND, 1.1
  - Spokane <2.6, <5.3
  - Tacoma ND
- Wisconsin
  - Madison 8.5
  - Milwaukee 4.0, 2.5

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[a] Data from Durfor and Becker.[131]

[b] ND = Looked for but not found.

TABLE 2-3 Nickel Content of Water in Ontario, 1970-1971[a]

Sample Source	No. Samples	Nickel Content, mg/liter[b]	
		Range	Mean
Surface water			
Muskoka area[c]			
Lake Vernon	11	0.00–0.15	0.01
Big East River	9	0.00–0.15	0.02
Trent River area[d]			
Trent River	3	0.00	–
Crowe River	6	0.00–0.12	0.06
French River basin[e]			
Lake Wanapitei[f]	4	0.00–0.14	0.07
Coniston Creek above Wanapitei River[g]	10	0.96–6.00	2.97
Coniston Creek at Hwy. 17 below Wanapitei River[g]	9	0.10–2.50	1.03
Emery Creek above Wanapitei River	6	0.10–1.60	0.68
Wanapitei River at Hwy. 17	16	0.00–0.18	0.07
Wanapitei River at St. Cloud[h]	12	0.00–5.00	0.58
Spanish River basin			
Chaping River above High Falls	10	0.00–0.55	0.19
Chaping River above Levack	15	0.00–0.10	0.01
Roberts Creek	15	0.00–0.13	0.02
Vermilion River above Capreol	7	0.00–0.13	0.03
At Capreol below rail yards	15	0.00–0.16	0.02
At Hwy. 17	4	0.00–0.12	0.07
Copper Cliff Creek[i]	15	0.16–11.00	4.42
Junction Creek above Kelley Lake[j]	15	0.10–7.50	3.24
Junction Creek at outlet of Kelley Lake	15	0.12–3.70	2.18
Junction Creek downstream of Garson	7	0.00–0.47	0.18
Junction Creek above Sudbury	10	0.00–1.82	0.39
Meatbird Creek	1	2.82	–
Spanish River at High Falls	1	0.00	–
Gough Creek	1	0.00	–
Moore Creek below Levack[k]	10	0.00–5.00	0.95
Moore Creek below Falconbridge	14	0.00–0.30	0.13

Northwestern Ontario[l]			
Rainy River below Baudette River	4	0.00	–
Rainy River below Emo	6	0.00	–
Rainy River above Fort Frances	8	0.00–0.04	0.005
English River at Manitou Falls	13	0.00–0.40	0.06
Red Lake	1	0.00	–
Snib Lake	1	0.00	–
Balmer Creek	1	0.33	–
Chakuni River	1	0.00	–
Port Colborne area[m]			
Ditch I–Fares St. and Lake Road	26	0.00–1.10	0.08
Ditch II–Inco outfall	27	0.00–14.80	5.77
Welland River	1	0.10	–
Drinking water			
Toronto[n]			
R. L. Clark Water Works	1	<0.05	–
R. C. Harris Water Works	1	<0.05	–
Lakeview Water Works	1	<0.05	–
Barrie			
Municipal Water Works[o]	1	0.0	–

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[a] Information from the Water Quality Monitoring Program, Ministry of the Environment, Toronto, Ontario, Canada, for the period January, 1970–September 1971.

[b] Atomic-absorption method.

[c] Cottage Lake resort area, north central Ontario.

[d] Resort area, southern Ontario.

[e] Resort and fishing camps, northern Ontario; some parts of this river basin near mining and refining areas.

[f] About 20 miles northeast of Sudbury; nickel mining areas.

[g] Nickel processing (sinter) plant in Coniston.

[h] Resort and logging area in northern Ontario; one large pulp mill.

[i] Copper Cliff Mining and Refining.

[j] Near nickel mining and refining activities.

[k] Levack, a nickel mining town.

[l] Resort area; camping and fishing; lumbering.

[m] Nickel refining in Port Colborne on Lake Erie shore.

[n] Lake Ontario water.

[o] Well water.

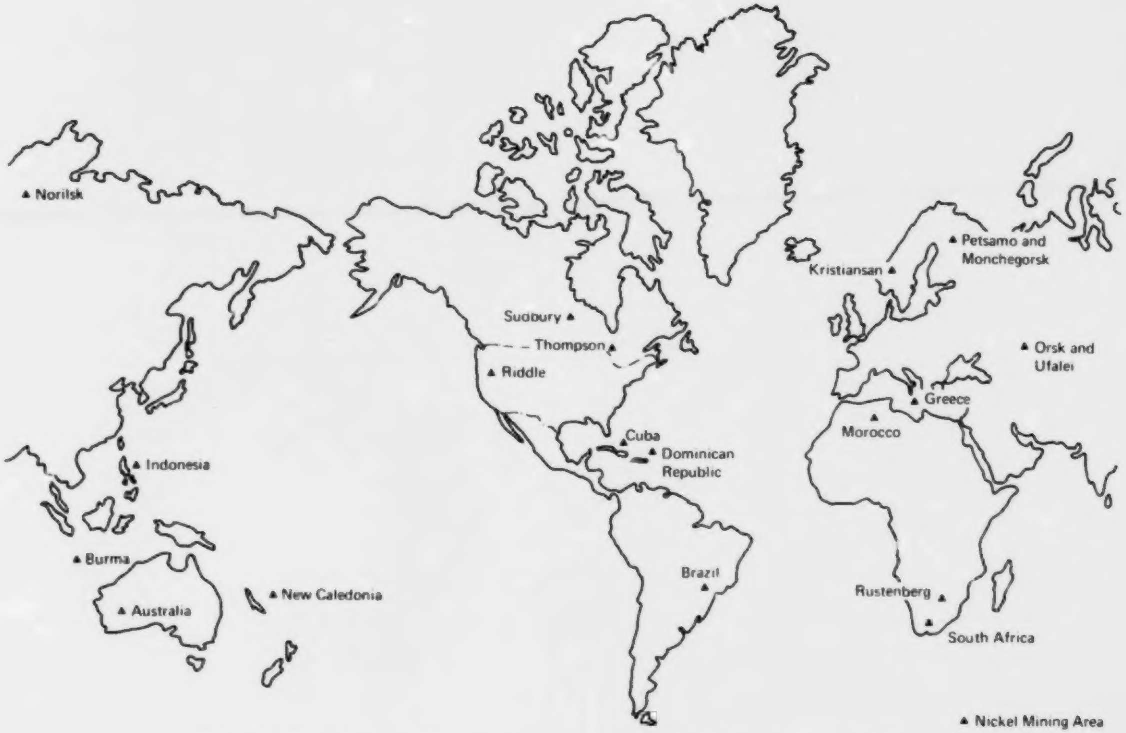

FIGURE 2-3 Principal nickel-producing areas of the world. Data from Howard-White.[255]

TABLE 2-4 Nickel in U.S. Drinking Water, 1969–1970[a]

Nickel Content, mg/liter	No. Samples	Nickel Frequency, % of Samples
0.000	543	21.69
0.001–0.005	1,082	43.22
0.006–0.010	640	25.57
0.011–0.015	167	6.68
0.016–0.020	46	1.84
0.021–0.025	14	0.56
0.026–0.030	4	0.16
0.031–0.035	2	0.08
0.036–0.040	1	0.04
0.041–0.045	1	0.04
0.046–0.050	1	0.04
0.051–0.055	1	0.04
0.075	1	0.04
TOTAL	2,503	100.00

[a] Comprises 969 water supplies, representing all water supplies in eight metropolitan areas and one state. Data from Leland J. McCabe (personal communication).

Mining and Concentration of Ore

The nature of occurrence of nickel ore divides the nickel extraction industry into two broad segments. Sulfide ore is mined chiefly underground; the nickel minerals are concentrated by physical methods, and the concentrate in most instances is smelted pyrometallurgically. Oxide ore is mined in open pits; the nickel minerals cannot be concentrated by physical means, and the nickel must be extracted either in a chemical form by leaching or in the form of ferronickel by smelting. The cobalt that occurs with nickel normally stays with it through smelting and to the last stages of leaching. However, in instances in which the cobalt would be deleterious to the nickel's ultimate use, the two are separated for production and sale of the more valuable cobalt.

Underground nickel ore, characterized by sulfide minerals, is crushed and ground to a grain size that liberates these minerals. Then the sulfides are concentrated by differential-flotation processes to make a nickel concentrate, a copper concentrate (principally chalcopyrite), and an iron concentrate (principally pyrrhotite).

Nickel oxide laterite mines are open pits, on or near the surface. The deposits seldom exceed 60 ft in depth, so the mines cover large areas. Power shovels, drag lines, and other mechanical devices are used for loading. First transportation in the pits is normally by trucks or conveyor belts, which deliver the ore to a railroad, continuous car conveyors, or aerial tram-loading pockets for transportation to the processing plant.

TABLE 2-5 Estimated World Nickel Production by Country[a]

Country[b]	Nickel Production, tons		
	1969	1970	1971
Australia (concentrates)	12,324	31,862	34,000
Brazil (ore)	1,900	3,200	3,500
Burma (speiss)	33	23	20
Canada[c]	213,611	305,881	293,947
Cuba			
Oxide	20,400	20,400	40,000
Sulfide	18,400	18,400	
Finland			
Concentrates	3,996	5,634	4,968
Nickel sulfate	211	165	165
Greece (recoverable ore)	9,115	9,500	11,600
Indonesia (ore)[d]	8,404	19,842	29,762
Mexico (ore)	39	49	55
Morocco (nickel ore and cobalt ore)	311	152	220
New Caledonia (recoverable)[e]	99,731	116,164	112,751
Norway (concentrate)	273	360	360
Poland (ore)	1,650	2,200	2,000
Rhodesia, Southern (concentrate)	4,400	12,000	13,000
South Africa, Republic of (electrolytic)	11,000	12,739	14,067
USSR (ore)	115,000	120,000	130,000
United States			
Byproduct of metal refining	2,714	2,909	2,581
Nickel recovered from domestic ore	13,096	12,649	13,073
TOTAL	536,608	694,129	706,069

[a] Derived from Reno.[495]

[b] Insofar as possible, this table represents mine production of nickel. Where data relate to some more highly processed form, the figures given are used as a measure of mine output, in lieu of actual reported mine output. Such countries as Czechoslovakia, Japan, and North Korea, which produce smelter nickel from imported raw materials, have been excluded to avoid double counting. In addition to the countries listed, Albania and East Germany also produce nickel from mines, but available information is inadequate for reliable estimates of output.

[c] Refined nickel and content of oxides and salts produced, plus recoverable nickel in matte and concentrates exported.

[d] Includes a small amount of cobalt not recovered separately.

[e] Nickel–cobalt content of metallurgic-plant products plus recoverable nickel–cobalt in exported ores.

The Hanna Mine at Riddle, Oregon, the only nickel mine in the United States, is served by an aerial tram that delivers the ore directly to a blending stockpile.

Smelting and Refining of Concentrates

The copper concentrate is treated in a conventional copper smelter for recovery of copper by a process that does not differ from that used to treat the copper sulfide concentrates produced at copper mines. Some of the nickel stays with the copper through the smelting process and is separated when the copper is refined electrolytically; nickel remains in the electrolyte at copper refineries and is recovered when it accumulates to the tolerable limit of 20 g/liter. High-grade nickel sulfide concentrate can be roasted to form a nickel oxide, which is then smelted with petroleum coke as a reductant to produce a nickel anode that is refined electrolytically into pure nickel cathodes, an item of commerce.

Nickel sulfide concentrates are smelted with a flux to obtain a copper–nickel–iron matte (matte is a combination of a metal with sulfur). The furnace matte is treated to remove iron slag and part of the sulfur as sulfur dioxide gas, producing a sulfur-deficient copper–nickel Bessemer matte. In one major operation, this matte is cooled slowly to facilitate grain growth of crystals of copper and nickel sulfides and a nickel–copper alloy containing the bulk of the precious metals. The crystal mass is pulverized to liberate the components from each other. Nickel–copper alloy is extracted magnetically and then refined electrolytically. Nickel–copper sulfide minerals are separated by flotation. In one process, the nickel sulfide concentrate is treated by selective leaching with ammonia under pressure and then heating of the pregnant solution to precipitate copper. Nickel and cobalt are recovered separately as metal powders by hydrogen reduction of the purified pregnant solution.

Nickel is also recovered from nickel sulfide by the carbonyl process. The nickel sulfide, NiS and/or Ni_3S_2, is roasted to produce the oxide, NiO. Oxygen can be added to raise the temperature and speed the reaction. Nevertheless, all nickel oxidation states and the insensible gradations between may be formed during the process. The nickel oxide is reduced with water gas to form crude sponge nickel, which is treated with carbon monoxide to form nickel carbonyl, $Ni(CO)_4$. The carbonyl is decomposed by heat at atmospheric pressure to make nickel pellets or nickel powder. The iron sulfide concentrate that is a residue of the nickel carbonyl process contains some nickel; it is therefore roasted to remove the sulfur as sulfur dioxide gas and then selectively reduced in gas-fired rotary kilns in a controlled reducing atmosphere. The kiln product is leached with ammonium carbonate to recover the nickel as nickel carbonate, which is refined to nickel oxide for market.

Basically, then, the pyrometallurgic treatment includes five types of operation: concentrating, roasting, smelting, converting, and refining. The roasting process generates a metallurgic smoke that consists of gases, dust, and fume. The gases commonly contain nitrogen, carbon monoxide, carbon dioxide, water vapor, oxygen, and sulfur oxides. The dust composition depends on the type of material being roasted and consists of

TABLE 2-6 U.S. Consumption of Nickel (Exclusive of Scrap) by Use and Form, 1972[a]

Use	Form, tons					
	Commercially Pure Unwrought Nickel	Ferro-nickel	Nickel Oxide	Nickel Sulfate and Other Salts	Other Forms	Total of Figures Shown
Steels						
Stainless and heat-resisting	17,155	16,788	11,196	–	227	45,366
Alloys (excludes stainless)	7,930	5,004	6,408	–	213	19,555
Superalloys	11,536	251	49	–	436	12,272
Nickel–copper and copper–nickel alloys	8,307	–	36	–	199	8,542
Permanent magnet alloys	3,925	221	54	–	–	4,200
Other nickel and nickel alloys	27,873	269	698	5	49	28,894
Cast irons	2,825	272	401	–	938	4,436
Electroplating[b]	25,351	–	31	3,547	107	29,036
Chemicals and chemical uses	906	–	71	204	–	1,181
Other uses[c]	4,614	1	371	183	635	5,804
TOTAL (reported by companies canvassed and estimated)	110,422	22,806	19,315	3,939	2,804	159,286

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[a] Derived from Reno.495

[b] Based on monthly estimated sales to platers.

[c] Includes batteries, ceramics, and other products containing nickel.

the original, partially reacted fine particles of the concentrate, furnace lining, and fuel. The fume is the part of the solid material that has been volatilized, sublimed, and later condensed. An example of flue-dust composition for a nickel refinery is given in Table 2-7. It is not known whether this analysis is representative of flue dusts from other nickel refineries.

Effluents from the smelters and converters differ little from those emitted from the roasters. Normally, however, they are at higher temperatures than those from the roasters and may not contain as large a percentage of the sulfur oxides if smelting and converting are preceded by roasting.

In a well-operated nickel electrolytic refining operation, there is no visible effluent to the atmosphere. The system is open, however, and there is a measurable loss of water in electrolyte through evaporation.

Nickel oxide laterite ore is processed by smelting to produce an iron–nickel matte, smelting to produce ferronickel, leaching with ammonia, or leaching with sulfuric acid.

In the first method, the ore is dried; impurities are removed by screening; and smelting with coke, limestone, and gypsum forms an iron–nickel matte, which is processed in the same way that the mattes with similar composition are smelted and refined in the treatment of sulfide ore.

In the second method, the ore is smelted with coke and limestone or other carbon reductant to produce ferronickel, which is refined by dephosphorizing it and removing silicon and chromium in a slag. The ferronickel so produced is an item of commerce. Ferronickel that is produced in the United States by smelting is roasted or calcined before

TABLE 2-7 Analysis of Flue Dust from an Ontario Nickel Refinery[a]

Compound	Fraction, %
Cupric oxide, CuO	3.4
Nickel sulfate, $NiSO_4 \cdot 6H_2O$	20.0
Nickel subsulfide, Ni_3S_2	57.0
Nickel oxide, NiO	6.3
Cobalt oxide, CoO	1.0
Ferric oxide, Fe_2O_3	1.8
Silicon dioxide, SiO_2	1.2
Miscellaneous	2.0
Moisture	7.3
TOTAL	100.0

[a] Derived from Gilman.[196]

being charged to an electric furnace. Ferrosilicon is used as a reducing agent.

In the two leaching methods, the ore is prepared by crushing, grinding, screening, and drying. Then the cobalt and nickel are reduced with producer gas, and the ore is leached in four stages with an ammoniacal ammonium carbonate solution or leached with sulfuric acid. In the former instance, the carbonate is calcined to obtain nickel oxide, which is sold as an item of commerce or further refined in the same manner as oxides obtained from sulfide ore. In the latter instance, the ore is preheated with high-pressure steam to about 475 F. The acidic solution is neutralized with coral mud, and then nickel and cobalt are precipitated as sulfides with hydrogen sulfide. The crude sulfide precipitate is leached under oxygen pressure in a weak acid solution to redissolve the nickel and cobalt. The resulting solution is neutralized with ammonia and purified, and nickel and cobalt powders are recovered by hydrogen reduction under pressure.

Dust is generated in loading, in transporting, and in the blending and drying yards. Gases, dust, and fume are emitted from the smelting furnaces, just as they are emitted from the furnaces that smelt sulfide ore. However, in furnaces that produce ferronickel, the sulfur oxide emissions are not as much of a problem. The ammonia and sulfuric acid leaching systems are in a closed circuit from which there is no emission to the atmosphere. The precipitated nickel carbonate is roasted to remove carbon dioxide, and this process carries some nickel oxide to the atmosphere.

Because the inhabitants of the island of New Caledonia have been involved in the mining and refining of nickel for about 100 years, studies of these people should be a valuable source of information on the effects of nickel on man and his environment. The island is covered with lateritic deposits derived from the underlying rock. Nickel ore has been mined in New Caledonia since 1866 and smelted there since 1875. Essentially all phases of mining, transporting, drying, leaching, and smelting of serpentine ores are exemplified by the nickel industry on the island. Unfortunately, neither the government nor nickel producers have kept detailed health records of the general population or of the workers in the nickel industry.

Melting and Casting of Alloys

Melting to produce alloys may be performed in any of a number of types of furnace:

open-hearth furnace: steels
reverberatory furnace: copper, nickel, and other nonferrous metals
basic-oxygen furnace: steels (heat is evolved by the reaction of the molten charge from the blast furnace with the impinging oxygen lance)
electric-arc furnace: steels, iron-base alloys
electric-induction furnace: any alloy
cupola: cast iron, including nickel–alloy irons

In the broad sense (but particularly with regard to the open-hearth and electric-arc furnaces), the cold charge to a furnace consists of limestone (to form a slag to absorb impurities), iron oxide as ore or mill scale (to oxidize the impurities), steel scrap, and alloy scrap. (In some operations, molten pig iron from the blast furnace is charged later, but this need not be dealt with here.)

The period of meltdown and oxidation of the heat* is the most critical period during the entire melt cycle, from the standpoint of emission to the atmosphere. In the electric-arc process, there is intense creation of oxide fumes as the arc both burns and melts the solid scrap. The result is a dense brown plume of oxide rising from the furnace roof to the overhead hoods of the essential dust-collection system. The open-hearth furnace produces similar emission when enough melt has formed to achieve a reaction with the limestone and iron oxide, giving rise to a vigorous boil of escaping carbon dioxide. With dust and fume, this is carried along by the gases of combustion, passing through the "checker works" (the regenerative system for preheating gas and air before combustion) to the dust collectors and the stacks. In the electric-induction furnace, there is occasional moderate sparking between adjacent pieces of scrap, but there is much less production of dust than in either the open-hearth or electric-arc furnace. In the cupola, air is blown into the furnace through the tuyeres and up through the charge, generating heat by reaction with the coke in the charge. This process probably has less control of emission than any other; the cupola usually discharges its carbon dioxide, dust, and fume directly into the atmosphere with no attempt at dust collection.

After completion of the meltdown and the oxidation period (which should have driven most impurities into the slag and the carbon to the furnace gases as carbon dioxide), the melt is covered with a blanket of molten slag, whose major ingredients are lime, silica, and iron oxide.

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* "Heat" here refers both to the mass of metal produced by the furnace in a single melt and to the melting cycle itself.

The reduction period—involving additions of ferromanganese, ferrosilicon, etc., to deoxidize the melt—generates little in the way of dust and fume.

At the end of the reduction period, last-minute adjustments of carbon and alloy contents are made on the basis of chemical analyses, and the final deoxidation is achieved. This is done either just before or during tapping of the heat into the ladle, depending on the additions used. These may be ferrosilicon, aluminum, calcium–silicon, or some combination thereof. Relatively little fume is emitted at this stage.

The preceding paragraphs are related to melting of steel and iron alloys. Nonferrous melting is commonly done in reverberatory furnaces, crucible furnaces, or induction furnaces (either high-frequency or low-frequency). In the latter, the melt forms the secondary coil of a transformer, and only a portion of the available melt is tapped at the completion of each heat. In most nonferrous melting, the temperatures are much lower and dust collection is easier. The metal being melted is usually more valuable, and this offers an incentive to minimize losses to the atmosphere.

Nickel-base alloys comprise two categories. The first includes the high-nickel alloys, such as "A" nickel (99.4% nickel and cobalt), "D" nickel (95% nickel and 4.5% manganese), "Z" nickel (94% nickel and 4.5% aluminum), several grades of Monel (basically 63–67% nickel, 30% copper, and minor additions), and a number of grades of Inconel (high nickel, approximately 13% chromium, and various additions, such as molybdenum, columbium, and aluminum); most of these are melted almost exclusively at the relatively few nickel-producing sites. The second category includes a wide variety of heat-resistant or "super" alloys designed to withstand very high temperatures and still retain appreciable strength. These are produced at many locations not related to nickel production. These alloys are often produced by melting in air in induction furnaces (although arc furnaces are used in some shops), but many are prepared *in vacuo*, using either arc, induction, or electron-beam melting. In any of the latter procedures, there are minimal releases to the atmosphere.

Melting at nickel-producing sites, such as Sudbury, Ontario, has produced emission of nickel, as evidenced by the data in Table 2-8, which compares air-sampling results obtained in Toronto, Simcoe, and St. Catharines, Ontario, with results from the Sudbury area. Emission of nickel also occurs from the nickel refinery at Huntington, West Virginia. A 1968 report[272] compared ambient-air nickel concentrations from seven sampling stations in Ironton, Ohio; Ashland, Kentucky; and Huntington, West Virginia. The concentration near the Huntington, West Virginia, plant was 1.2 $\mu g/m^3$, whereas the average of the other six stations was 0.04 $\mu g/m^3$.

There is uncertainty regarding the quantities of nickel emission from metallurgic melting, such as iron and steel plant operations. Although the National Air Sampling Network (NASN) has reported for several years the concentrations of suspended particles and of various elements, including nickel, throughout both the urban and the suburban regions of the United States, few data appear to be available regarding actual emission from iron and steel plants. There has been a report[479] describing operating problems with a dust-collection system at the Butler Works (in Butler, Pennsylvania) of the Armco Steel Corporation. This plant melts a variety of alloys in a large electric furnace, melting heats of 70 tons. The sludge collected from the scrubber during periods in which chromium–nickel steels are being melted contains 35% iron, 9.5% chromium, and 2.5% nickel. Presumably, all are present as oxides, perhaps in combination with calcium oxide and silica. Sampling of the "clean air" released by the scrubber during the oxygen-blow period of chromium–nickel heats showed that it contained, at about 60 mg/m^3, material assumed to be comparable with the sludge. This implies that nickel is carried by this "clean air" at 1.5 mg/m^3.

The actual loss of nickel in melting has been known for many years to be low. The effect of this over the years has been to increase slowly the average amount of nickel in unalloyed carbon steel because of inadvertent additions of nickel-bearing scrap to the furnace charge from time to time. This nickel is retained during melting, and each occurrence adds to the residual nickel in carbon steel, now commonly about 0.15% nickel. This phenomenon was particularly prominent in the years before the introduction of the oxygen lance. Alloys were normally added after the oxidizing stage of the heat, and the bath was protected thereafter by the layer of slag. Nickel, being chemically negative to iron, would remain in the bath, rather than establish a nickel oxide concentration in the slag in common with iron and chromium. In electric-arc melting of heats, in which chromium–nickel alloy scrap is essential, some nickel is undoubtedly lost in the fume created during meltdown. The amount of fume is small, however, compared with that created in melting other types of steel.

A review of steel-melting processes[561] discusses the relative effectiveness of various methods of dust collection—electric precipitators, baghouse collectors, and water scrubbers. The last is probably the least efficient, because it tends to collect only the larger particles, letting the finest escape. Even in the best systems, the outlet gases have been found to carry particulate matter at approximately 5 mg/m^3.

TABLE 2-8 Ambient-Air Nickel Concentrations, μg/m^3, 1971[a]

	Toronto												Sudbury	
Date, month/day	67 College St.	360 Christie St.	Hwy. 401 and Pharmacy	Kennedy and Lawrence	Redland Crescent	Science Centre	Bathurst and Wilson	Rathburn and Benforth	Queensway Hospital	Evans Ave.	Simcoe	St. Catharines	Ash St.	50 Cedar
1/15	–	0.041	0.033	0.006	0.026	0.020	0.057	0.044	0.054	0.037	–	–	0.076	0.177
1/28	0.068	0.042	0.008	–	0.026	0.024	0.036	0.008	0.024	0.025	0.004	0.016	2.009	–
2/9	0.048	0.058	0.028	0.011	0.014	0.013	0.022	–	0.009	0.018	0.070	0.009	0.110	0.083
2/26	0.053	0.023	0.033	0.028	0.043	–	0.035	0.011	–	0.010	–	–	0.752	–
3/10	0.107	0.047	0.035	0.059	1.164	0.019	0.044	0.034	0.025	0.078	–	0.039	0.785	0.916
3/25	0.030	0.031	–	0.006	0.008	0.025	0.015	–	0.034	0.015	–	0.007	1.339	1.144
4/10	0.035	0.036	0.006	–	–	0.020	0.015	0.006	0.047	0.016	–	0.009	0.278	–
4/25	0.039	0.023	0.014	–	0.008	0.020	0.016	–	0.027	–	–	–	0.035	0.150
5/10	0.026	0.033	0.006	–	0.008	0.020	0.008	–	0.008	0.039	0.021	–	0.984	0.785
5/28	0.058	0.020	–	0.006	0.035	–	–	0.006	0.008	0.016	0.017	0.043	0.044	–
6/10	0.080	–	0.014	0.018	0.017	0.023	0.026	0.029	0.021	–	0.017	0.038	0.669	0.615
6/25	0.047	–	–	0.028	0.021	0.039	0.035	0.033	–	–	0.023	0.031	0.662	0.392
7/10	0.060	–	0.017	0.024	0.032	0.050	0.048	0.039	–	0.058	0.037	–	1.327	–
7/24	0.069	–	–	0.029	0.022	0.064	–	0.036	0.045	0.058	0.066	–	1.303	–
8/8	0.115	–	–	–	–	0.037	0.039	–	0.034	0.055	0.011	–	1.272	–
8/20	0.016	–	–	–	–	–	0.031	0.025	0.020	0.043	0.015	–	0.730	–

[a] Information from the Air Management Branch, Ministry of the Environment, Toronto, Ontario, Canada.

The loss of nickel during the casting of nickel-bearing steels is believed to be low and not to result in significant air pollution. The exposure to the air is brief, and nickel tends to remain with the melt and not be oxidized.

Forming and Fabrication of Alloy Shapes

On completion of the melting cycle, the heat is tapped into a large ladle and poured into ingot molds. After solidification of the metal, but while it is still at a high temperature (only in special circumstances are ingots cooled to ambient temperatures), the ingots are withdrawn from the molds by a mechanical "stripper" and transferred to a furnace (termed a "soaking pit" in this case) for reheating and temperature equalization in preparation for hot working. Oxidation during these phases of processing is normally by the formation of surface oxide layers, or "scale." This scale is only loosely adherent to unalloyed-steel shapes; but when a nickel alloy is involved, the formation of scale is retarded, and it is much more adherent. No air-sampling data appear to be available, but nickel emission to the air is considered minimal.

HOT WORKING

The conversion of the ingot to a useful shape takes place by a sequence of hot-working reductions of cross section that vary with the intended shape. The ingot may be either rolled or forged by stages to successively smaller cross sections, with reheating as necessary to maintain adequate plasticity. In some circumstances, the intermediate product is cut to suitable billet lengths and then extruded to some desirable contour as, for instance, seamless tubing. Data on particulate emission to the air are not available, but the situation is generally similar to that of ingot handling. No serious loss of nickel to the air is likely. One exception deserves consideration: The surfaces of partially rolled shapes are sometimes treated for the removal of mechanical defects (laps, rolled-in scale, etc.) by grinding or flame scarfing with an acetylene torch. This latter is a combined burning and melting procedure that may be performed in the open. The contributions to air contamination are not known but may be appreciable locally.

GRINDING

At many stages during metallurgic processing, it is necessary to condition the metal surfaces by grinding, polishing, or buffing. Cast shapes are ground to produce an appropriate surface contour after removal of gates and risers. Welded assemblies are ground to provide a smooth contour at joints. Some grades of metal sheet are polished to a high finish. All these operations create tiny metal particles, which, when dry, are potential air contaminants. Polishing is usually done when the metal is wet and does not appear to be a source of particulate emission. Grinding-wheel stations are normally provided with adjacent hoods that exhaust to dust collectors, and the workmen usually wear respirators.

WELDING

Assembled shapes are fabricated largely by welding, which can be manual or automatic and may use electric-arc, electric-spot, oxyacetylene-torch, or furnace-brazing techniques. Preparations for welding often require grinding, which does not differ from that already discussed. Spot welding is rapid and brief and normally would not be considered a source of any appreciable fume. There is, however, a definite local flash as the metal is heated; and, where many units are in operation, as in an automotive assembly line, more particles may be emitted than has been realized. Sizable emission to the environment outside the plant appears unlikely. Furnace brazing uses a reducing atmosphere to avoid surface oxide films that would prevent "wetting" of the joints by the brazing alloy. This operating condition should preclude the release of nickel to the air. Arc or torch welding requires that rod and base metal be melted on a highly localized scale. In some techniques, a protective or inert-gas atmosphere surrounds the bead being melted; in others, there is a slag cover. In all cases, fume is undoubtedly produced, some of it consisting of volatilized components of the weld-rod coating; if work is done in the open without dust-collecting equipment, it appears desirable to sample the air to determine the workmen's exposure.

POWDER METALLURGY

Many parts can be formed by compaction and sintering of metal powders, if the number desired is too great to justify the cost of individual machining but not great enough to justify the cost of preparing forging dies. Carefully sized powders are formed into a "green" compact under high mechanical or hydraulic pressure and then heated to high temperature in a reducing atmosphere to sinter the particles together and achieve maximal density. The operations are sometimes combined, pressing the powder to final size in carbon dies at very high temperature.

Nickel powder may be produced by a number of methods. In "steam shattering," little used today, a stream of molten nickel flowing from a furnace is "shattered" into droplets by a steam jet over a water tank. This technique, with its abrupt quench, probably contributes little to airborne nickel concentrations, but no data seem to be available. In any case, it does not appear to be a contributor at this time.

The Mond process, developed at Clydach, Wales, is well known. Nickel powder is formed from crude nickel by exposing it to carbon monoxide gas at a carefully controlled temperature, forming nickel carbonyl gas. This gas is diverted to a decomposition chamber, where the temperature is raised to decompose the gas and grow tiny nickel particles whose surface characteristics are reminiscent of those of chestnut burrs. Two varieties of nickel carbonyl powder particles are illustrated in Figure 2-4.

Before World War II, nickel carbonyl powder was produced only at the Clydach plant in Wales. Shortly after the war, a second plant was constructed at Huntington, West Virginia, and additional facilities have since been erected elsewhere. The newest is at Copper Cliff, Ontario, with an annual capacity of 62,500 tons of nickel carbonyl.

Nickel powder may also be prepared by crushing and grinding. Final sizing has been done on occasion by ball milling. Any crushing procedure would require dust-collection equipment, which should be highly effective, in that there would be no problem of handling high-temperature gases, as in treating fume from a melting furnace. Ball milling is done in a relatively tight system. No data are available, but both the losses of nickel to the atmosphere and the volume of powder produced by this procedure are deemed insignificant.

The most important use of nickel powder is in the manufacture of special small parts of heat-resistant alloy by blending iron, chromium, and nickel powders in the desired proportion. The principal opportunity for loss of nickel to the air would be in the preparation of the blends. No specific data have been obtained, but it is believed that this operation is always well contained and does not contribute significantly to air pollution.

ELECTROPLATING

Preparation for electroplating normally involves grinding, shot or grit blasting, polishing, etc. These are sources of dust no different from those in any foundry or mill operation, and the conventional means of dust control are necessary.

Nickel electroplating is very widely used: consumption of nickel for this purpose was 24,550 tons in 1970 and 20,728 tons in 1971.[495]

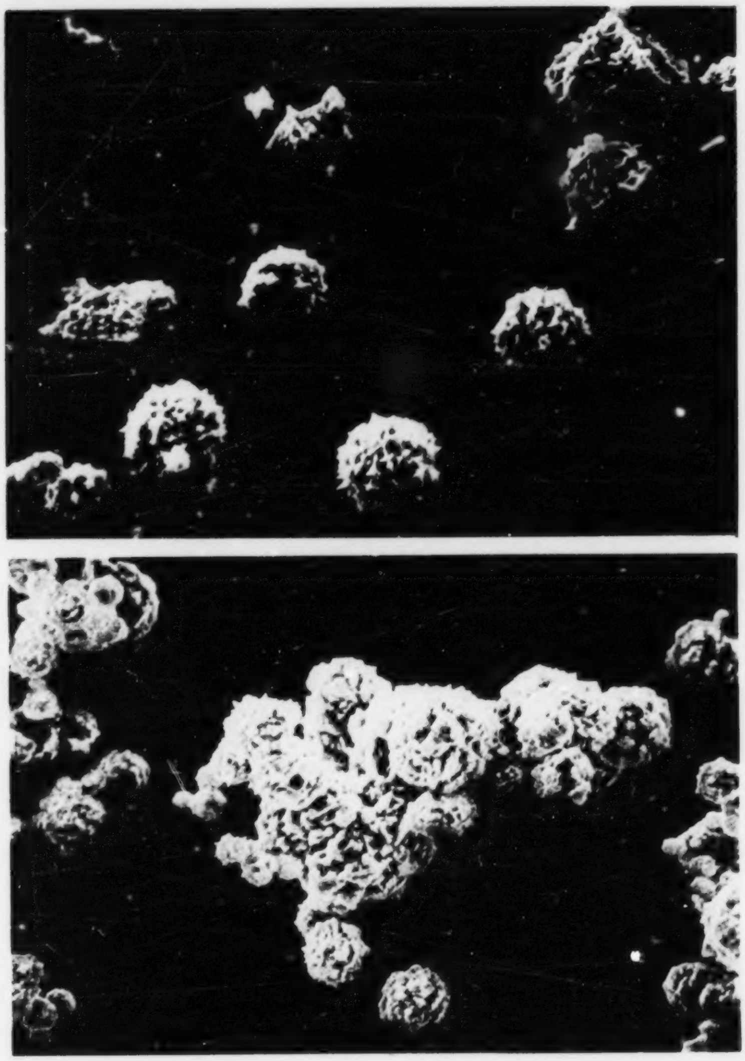

FIGURE 2-4 Top: Scanning electron micrograph of type 123 nickel carbonyl powder. The smallest particle shown is approximately 1.5 μm in diameter. Bottom: Scanning electron micrograph of type 100 nickel carbonyl powder. Courtesy, Dr. E. N. Skinner, The International Nickel Co., Inc.

Electroplating within the United States accounts for approximately 16% of the country's total annual nickel consumption. Data on its contribution to air pollution are sparse. Sullivan[581] remarks that, "although nickel platers have been observed to develop deleterious health effects from apparent exposure to nickel particulates or mists, no information was found on the emission rates of nickel from plating facilities."

The evidence suggests that the major problems in nickel electroplating are the effects of toxic materials on the workmen (dermatitis, eye injuries, chemical and thermal burns from splashes, and inhalation of fumes, mists, and vapors) and are not related to emission to the general atmosphere.

NICKEL–CADMIUM BATTERIES

Friberg[173] reported in 1948 that air concentrations of nickel dust from 10 to 700 mg/m^3 had been measured in an alkali-storage-battery plant. The effect of this extremely high exposure was obscured by the history of simultaneous exposure to cadmium. More data are obviously needed in assessing the hazards from production of nickel–cadmium batteries in the United States and Canada.

ELECTRONICS AND COMPUTERS

Nickel is used in electronic devices in the following forms:

stainless-steel brackets, panels, screws, etc. (typically containing 8% nickel)
electroplating on chassis and other hardware
supports or leads in vacuum tubes (40–100% nickel)
transistor cans (100% nickel)
electric resistance wire (containing up to 80% nickel)
glass-to-metal seals (29–52% nickel)
magnets, including cores, laminations, and shields (50–80% nickel)
thermocouples (90–95% nickel)

The exact amount of nickel used in such forms is unknown; it is less than 25,000 tons a year and probably closer to half that amount.

It is difficult to imagine how nickel could be released to the environment during normal operation of electronic equipment. Abnormal operations involving arcing can vaporize nickel and other metals, but such incidents are infrequent and unpredictable.

Losses by Corrosion

Nickel alloys, both wrought and cast, are highly resistant to corrosion in natural environments and therefore do not present toxic possibilities, except in special circumstances. Nickel alloys used in acidic or caustic environments are designed especially for the purpose and therefore do not corrode at rates that would introduce significant amounts of nickel into the environment. In engineering practice, the nickel alloys and stainless steels, because of their relative cost, are seldom used in corrosive environments, unless the rate of attack is low enough to ensure an economic lifetime of the equipment. In general, the nickel alloys are not used if the corrosion rate exceeds 1 mil/yr; but in unusual circumstances, a nickel-bearing alloy may be used in an environment in which the expected corrosion rate is as much as 10 mils/yr. Corrosion of more than 50 mils/yr is never acceptable.

Nickel-bearing metal surgical implants and specially designed prosthetic devices that are in direct contact with the human body for long periods may corrode at rates sufficient to produce toxicity. This problem is reviewed in detail in Chapter 6.

Commercial Chemicals

Commercial nickel chemicals are generally processed by wet methods that appear to offer little opportunity for dust emission. There do not appear to be specific data available that can typify what air or sewer losses may take place in the preparation or processing of nickel chemicals. It would be desirable to obtain data to determine the nickel concentrations in liquid wastes from plants preparing and using these materials.

Waste Disposal and Scrap Recycling

In the United States, 15,000–25,000 tons of nickel are recycled each year through copper smelters and refineries and through nonferrous metal foundries and manufacturing plants. Nearly all the nickel-bearing material (scrap) processed in these plants is nickel-, copper-, or aluminum-base alloy. The steel industry recycles about twice as much nickel as the copper and other nonferrous industries. Steel scrap is in the form of stainless steel or nickel-bearing steel alloy. Recycled scrap is usually melted and refined and then used to make alloys or steels similar in composition to those in which it entered the recycling process. Therefore, nickel-scrap recycling processes can be compared directly with the processes used on primary metal.

Disassembly of electronic equipment to recover silver and other precious metals directly is not economical, so the common practice is to introduce entire complex units into the recovery process. The usual procedure is to smelt the scrap into a copper bullion, obtaining a semirefined alloy that contains all the metals present initially. The furnace effluent is carefully washed to preclude the loss of volatile precious metals, and an insoluble slag is left behind. The bullion is treated in an electrolytic plant; the copper is largely plated out, and the solution is bled to stripping cells in which the nickel salts are crystallized for recovery. Platinum metals appear in the sludge. Recent tests at the Salt Lake City station of the Bureau of Mines indicated that nickel was undetectable (by atomic absorption or spectroscopy) in the effluent from smelting furnaces. Any problem of groundwater contamination due to dumping of electrolytes would parallel the problem of disposal of electroplating solutions; there is an economic incentive to conserve the valuable metals in those solutions.

Nickel forms a significant part of our industrial and municipal waste, but the technique for recovering the valuable metal constituents of these wastes, other than iron, has not yet developed sufficiently to carry the work much past the stage of laboratory research. Although complete data are not yet available on the nickel content of the waste material from any segment of our society, Bureau of Mines researchers have reported on the composition and characteristics of municipal-incinerator residues (Table 2-9).[298] The fine-ash fraction in six municipal-incinerator residue samples consistently contained 0.01% nickel.

In current studies of contamination on street surfaces, composite

TABLE 2-9 Nickel Composition of Remelted, Melted, and Smelted Metal Wastes from Municipal-Incinerator Residues[a]

Waste	Nickel Concentration, %
Cans	0.02–0.06
Massive iron	0.1 –0.6
Iron wire	0.05–0.2
Iron oxide products	0.02–0.09
Nonferrous metals in residues	0.02–0.6
Nonferrous metals from beneath furnace grates	0.03–0.08

[a] Derived from Kenahan *et al.*[298]

samples have been collected in streets of five cities by sweeping, washing, and collecting runoff from the surfaces with no seasonal adjustments. Three sections of each city (industrial, commercial, and residential) were sampled separately. The concentration of nickel as a surface contaminant was found to be 0.15 mg/ft^2 in commercial areas, 0.23 mg/ft^2 in residential areas, and 1.25 mg/ft^2 in industrial areas.

Study of nickel-particle size distribution in surface contaminants in San Jose, California, and Seattle, Washington, indicated that 27.5% of total nickel fraction by weight associated with each size range was 43 μm or smaller, 75% was 840 μm or smaller, and 25% ranged from 840 to 2,000 μm.

SOURCES INVOLVING NICKEL AS A MINOR CONSTITUENT

Many raw materials, such as coal and petroleum, have been shown to contain nickel when withdrawn from the earth. The important question is related to the degree and the form in which this nickel is released during the use of the raw materials.

Coal-Fired Power Plants

The presence of nickel in coal mined in the United States has been discussed earlier in this chapter. It may be helpful to restate the nickel content as parts per million of coal, rather than as the content of the ash:

Coal Source	Nickel in Coal, ppm
Eight eastern states	19.4
Seven midwestern states	27.5
Eight western states	5.3

Not all this nickel is contained in emissions to the atmosphere. Therefore, a very large coal consumption would be necessary to contribute significantly to air contamination.

The direct evidence of the contribution of nickel to the air from coal is provided by analyses cited by Sullivan[581] from a report by Cuffe and Gerstle and summarized in Table 2-10.

It is obvious that coal-fired power plants may emit appreciable quantities of nickel to the atmosphere, and careful control and monitoring are needed. In the broader picture, however, the combustion of fuel for power is two orders of magnitude less than that burned for space heating.

TABLE 2-10 Nickel Emissions from Coal-Fired Power Plants[a]

Boiler Type in Coal-Fired Power Plant	Nickel Emitted in Collected Fly Ash	
	μg/SCF[b]	μg/m³
Vertical	250[c]	8,800
Corner	130[c]	4,600
Front-wall	170[d]	6,000
Spreader–stoker	350[e]	12,400
Cyclone-fired unit	510[d]	18,000
Horizontally opposed	690[e]	24,400

[a] Derived from Cuffe and Gerstle.[198]
[b] SCF = Standard cubic foot.
[c] Fly-ash collector is cyclone separator followed by electrostatic precipitator.
[d] Fly-ash collector is electrostatic precipitator.
[e] Fly-ash collector is cyclone separator.

Combustion of Petroleum Products

DIESEL-ENGINE EXHAUST

There have been few direct measurements of diesel-engine exhausts, but the values in Table 2-11 are from Reckner *et al.*[493] These examples are from a 1967 stationary diesel engine (Amer. Marc. Inc., Model AC 1, one cylinder). Whether the data from today's diesel-truck exhausts are comparable is not known. These values are based on measurements of the particulate phase of the diesel-engine exhaust and do not include any nickel that might be present as nickel carbonyl in the vapor phase. Because the values given represent an appreciable emission rate, the release from diesel automotive exhausts should be tested both for total nickel effluent and for the concentration gradient over increasing distances from the source.

FUEL-OIL COMBUSTION FOR SPACE HEATING

The nickel contents of commercial fuel oils have been quoted as ranging from nearly zero to 20 ppm. There do not appear, however, to be data available regarding the nickel content of stack gases of heating plants. For a given area, the amount of fuel oil burned gives a clue to possible nickel emission, although not on a basis of quantity per volume of exhaust gas.

Fuel-oil consumption for space heating in the Manhattan area is 3.9

TABLE 2-11 Diesel-Engine Exhaust

Substance	Nickel Concentration, μg/g of particles
Bulk diesel fuel[a]	2
Exhaust-valve coke	10
Particulate sample[b]	10,000 (0.65 μg/min)
Particulate sample[c]	1,000
Particulate sample[d]	500

[a] N.Y. Central Spec. 1370-C, Grade 2.
[b] No load at 1,400 rpm.
[c] No load at 1,800 rpm.
[d] Half load at 1,800 rpm.

billion gal/yr. If the fuel oil weighs 7.5 lb/gal and its nickel content is 10 ppm, and if 25% of the total nickel content is released to the stack gases, a year's consumption of fuel oil would contribute about 73,000 lb of nickel to the Manhattan atmosphere. If this were spread evenly from October 1 to April 30 (212 days), the *daily release* would be some 345 lb of nickel. Specific data are needed concerning the particles borne by stack gases. This subject is considered in further detail later in this chapter.

Asbestos Processing

Nickel is a potential constituent of all naturally occurring asbestos. Most commercial asbestos occurs in veins in solid rock matrices that require blasting and crushing for recovery, whether from open-pit or underground mines. These, of course, produce dust, as does the crushing needed to facilitate fiber separation and recovery and the milling used to separate the discrete fibers. All these processes are dry, so fibrous dust is a byproduct of nearly every step of asbestos recovery and use. Complete analyses of these dusts are not available, but there is no doubt that some part of the nickel that was in the asbestos before it was mined is present in all the fibrous dusts (see Chapter 6).

Nickel as a Metallurgic Byproduct

In the refining of copper, for instance, nickel is often recovered as nickel sulfate from spent electrolyte withdrawn from the electrolytic tanks.

After the electrolyte is stripped of copper and arsenic, the liquor is concentrated by boiling until the free sulfuric acid content is 72–75%. On cooling, both nickel sulfate and ferrous sulfate crystallize out. These crystals are then redissolved, and the iron is oxidized and precipitated with calcium carbonate. The nickel sulfate can then be crystallized out and marketed, or it may be roasted to oxide and then reduced to metal. Only in the last instance does there appear to be an air-contamination hazard. The roasting and refining would result in the same possible emissions as those described elsewhere in this chapter. The wet process of preparing nickel sulfate does not appear likely to generate significant nickel losses to the air.

Chemical-Plant Operations

Nickel is introduced into petroleum-refining plants as an inherent element in much crude oil. According to Bureau of Mines engineers, petroleum is refined in a closed system, so there is little chance that nickel-bearing materials can escape to the atmosphere during refining. Exhaustive tests have indicated that nickel invariably remains with the heavier and higher-boiling-point fractions of the crude oil processed. Therefore, it is eventually concentrated in residual fuel oil and in asphalt. Nickel catalysts are used in petroleum refining, particularly in desulfurization, hydrocracking, and hydrotreating; but, because petroleum is refined in a closed system, there is little chance that the nickel catalytic material will escape to the atmosphere or reach the ultimate product.

Complex nickel heterogeneous catalysts are used in plants that produce raw materials, such as hydrogen, that are used in production of gasoline and other motor fuels. These plants are often not parts of petroleum refineries.

In the past, nickel has also been used as an additive in some petroleum fuels. However, on the basis of recent discussions with consultants and technical representatives of numerous petroleum companies, it may be concluded that nickel is not now used as an additive in petroleum fuels by the domestic petroleum industry.

MODES OF EXPOSURE OF MAN TO NICKEL

It has been emphasized that many industrial operations emit nickel to the environment. This section discusses other sources of environmental nickel and the degree of human exposure to it.

TABLE 2-12 Concentrations of Nickel-63 in Environmental Samples

Location	Sample Types	Dates	Concentration, disintegrations/min per gram, dry-wt basis
Eniwetok Atoll	Soil and clam kidneys	May 1954	7.5–158
Bikini Atoll	Soil and clam kidneys	May 1957–August 1964	9.8–163
Rongelap Atoll	Soil	September 1961	0.5–3.1
Christmas Island	Clam kidney	April 1962	0.9
Penrhyn Atoll	Clam kidney	April 1962	0.4
Northeast Pacific Ocean	Chaetognaths and squid	February 1964–August 1966	0.1–4.5
Aleutian Islands	Lichen	October 1965	0.18–0.35
Eastern seaboard of United States	Shellfish composite	August 1963	0.02

Air

VOLCANOES AND FUMAROLES

Nickel has been identified in volcanic gases and condensates in a few instances, but only rarely and under unusual collecting conditions.[634,710] The circumstances lead to the conclusion that the nickel had been picked up from the surrounding rocks and not emitted from the body of the melt in the gaseous state. However, the paucity of complete analysis of volcanic emanations leaves much room for speculation. Apparently, most investigators have been concerned almost entirely with the characteristics of major components, with only passing interest in traces of metallic elements. It may be that nickel has gone undetected in volcanic gases only because no one has looked for it.

Nickel was not found in important concentrations in comprehensive analyses of sublimates at volcanic fumaroles at Paricutin, Mexico; Valley of Ten Thousand Smokes, Alaska; Vesuvius, Italy; Popandijan and Herope, Indonesia; Hokpaido, Showorkinzan Urn Volcano, Japan; and Bezymyangl, Kamchatka, USSR. However, Zies reported 0.01% nickel in magnetite at the Valley of Ten Thousand Smokes in 1929, and Japanese scientists reported 1.64% nickel in potassium aluminum sulfate incrustations at Shirane Volcano, Japan, in 1956.[542,543,710,725]

NUCLEAR EXPLOSIONS

Small amounts of the radionuclide nickel-63 have been reported[41] as present in soil and marine life in the area of the Pacific Proving Ground as a result of the testing of nuclear devices. The measurements were based on specific radiochemical-separation techniques and later liquid-scintillation counting of disintegrations. The concentrations observed are summarized in Table 2-12. These concentrations are very low; none is as high as 165 disintegrations/min per gram, which would be equivalent to less than 0.002 ppb (see Table 2-13). There appear to have been no air measurements, which would be of equal interest in determining the exposures that might affect the human lungs, in contrast with the accumulations reported in Table 2-12. Beasley and Held[41] suggest, for instance, that the concentrations for Christmas Island and Penrhyn Atoll, measured in April 1962, resulted from the USSR nuclear tests in 1961. Whether the airborne concentrations were or are above the detection limits for a reasonable sample size and collection period is, of course, an important consideration.

Beasley and Held[41] also comment on the possible contribution of

TABLE 2-13 Conversion of Scintillation Counts to Parts Per Billion

$$\text{Weight of nickel-63} = \frac{(\text{total atoms})\,(\text{atomic weight})}{N}.$$

Total atoms = (disintegrations/min) (half-life) (2).

$$\text{Concentration} = \frac{[(\text{disintegrations/min})/(\text{gram})]\,(\text{half-life})\,(2)\,(\text{atomic weight})}{N}.$$

(2) (half-life) = (92 years) (365 days) (24 h) (60 min) (2) = 96.71×10^{6} min.

Atomic weight = 63.

$N = 6.06 \times 10^{23}$.

Using $D_{\max}$ as 165 disintegrations/min per gram:
$$\begin{aligned}\text{Concentration} &= \frac{(165)\,(96.71 \times 10^{6})\,(63)}{(6.06 \times 10^{23})}\\ &= \frac{100.53 \times 10^{10}}{6.06 \times 10^{23}}\\ &= 16.59 \times 10^{-13}\\ &= 0.00166 \text{ ppb}.\end{aligned}$$

nickel-63 to the marine environment from the Columbia River water used as the coolant for the Hanford, Washington, nuclear reactors. This is appraised as "an unimportant source" of nickel-63. A similar situation has been reported[132] as existing in Great Britain in regard to the effluent from the nuclear power station at Bradwell-on-Sea, Essex. Here the principal gamma-emitting radioisotopes were chromium-51, cesium-134 and -137, antimony-124 and -125, cobalt-60, zinc-65, cerium-144, and iron-59. Nickel-63 is not rated as "a significant fraction of the radioactive discharges" from this type of nuclear power plant. The comment is made, however, that, with the advent of second-phase advanced gas-cooled reactors, nickel-63 will be produced in larger amounts because of the use of stainless-steel fuel cladding.

It appears warranted to conclude that nickel-63 from nuclear reactors does not offer a toxicity hazard; there is, however, a radioactivity hazard, although slight.

URBAN VERSUS NONURBAN AIR CONCENTRATIONS

There is a growing mass of data testifying to the presence of nickel in the air throughout the United States—both urban and rural. These data are being supplemented by information from overseas. Stocks[569] has reported annual values for northern England and for Wales for 1956–1958. The highest nickel concentration listed was for Elland (approximately 17 miles southeast of Leeds): 0.205 μg/m³. This was attributed to special local industry that was not defined. Of the remaining test sites, a group of seven—Liverpool and six sites ringing it—had an average air nickel content of 0.0111 μg/m³. The individual values were: Flint, 0.0069 μg/m³; Wrexham, 0.0069 μg/m³; Chester, 0.0120 μg/m³; Liverpool, 0.0110 μg/m³; Burnles, 0.0135 μg/m³; Darwen, 0.0112 μg/m³; and Ormskirk, 0.0160 μg/m³. The most rural of the localities surveyed had averages of about 0.0012–0.0023 μg/m³. It is clear that there was a higher nickel contribution from urban sites than from nonurban, but there was no clarification as to what portion of the airborne nickel could be attributed to metallurgic sources. Another deficiency in the data is the lack of information on particulate matter collected.

Most of the original data for ambient-air nickel concentrations within the United States appear to have stemmed from three sources represented in six references.[309, 331, 390, 391, 629, 657] To cite one of these, nickel concentrations measured by National Air Surveillance Networks in particulate samples collected at 30 urban locations during 1957–1964 have been reported by McMullen[390] and have been supplemented by more recent data from Tabor (personal communication). These data have been presented for three periods: 1957–1960, 1961–1964, and 1965–1968. Earlier data are not quoted because of changes in sampling procedures. In summary, the findings were:

	1957-1960	1961-1964	1965-1968
Average nickel concentration, μg/m³	0.047	0.035	0.026
Average concentration of suspended particles, μg/m³	155	137	125

The individual values by cities for the three periods are shown in Table 2-14. Several interesting aspects of these data are evident. The concentrations of both suspended particles and airborne nickel show a steady downward progression in the overall averages for the three periods. Although there has been steady pressure recently on both industry and local municipal government to reduce air pollution, these data appear to be somewhat early to reflect this pressure. The trend may therefore be fortuitous.

Three cities have nickel concentrations that are particularly above average: Boston, 0.112 μg/m³; East Chicago, Indiana, 0.132 μg/m³; and Philadelphia, 0.078 μg/m³. The reason for this is not evident.

TABLE 2-14 Average Concentrations of Suspended Particles and Nickel at 30 Urban National Air Surveillance Networks Stations, 1957–1960, 1961–1964, and 1965–1968[a]

	Concentration of Particles, $\mu g/m^3$				Nickel Concentration, $\mu g/m^3$			
Station	1957–1960	1961–1964	1965–1968	Average	1957–1960	1961–1964	1965–1968	Average
Atlanta, Ga.	125	104	105	111.3	0.021	0.012	0.007	0.013
Baltimore, Md.	141	145	129	138.3	0.057	0.071	0.051	0.060
Boise, Idaho	114	90	80	94.7	0.037	0.006	0.003	0.015
Boston, Mass.	156	144	98	132.7	0.171	0.076	0.090	0.112
Chattanooga, Tenn.	246	199	152	199.0	0.024	0.018	0.012	0.018
Charleston, W. Va.	217	271	226	238.0	0.058	0.040	0.015	0.038
Chicago, Ill.	190	170	122	160.7	0.044	0.043	0.033	0.042
Cincinnati, Ohio	145	131	131	135.7	0.024	0.018	0.013	0.018
Cleveland, Ohio	165	135	122	140.7	0.035	0.027	0.015	0.026
Columbus, Ohio	154	106	106	122.0	0.045	0.024	0.019	0.029
Denver, Colo.	139	146	126	137.0	0.021	0.028	0.007	0.19
Des Moines, Iowa	174	128	121	141.0	0.016	0.010	0.007	0.011

Detroit, Mich.	139	125	155	139.7	0.037	0.020	0.033	0.030
East Chicago, Ind.	206	218	181	201.7	0.202	0.123	0.070	0.031
El Paso, Tex.	224	156	–	190.0	0.015	0.015	–	0.015
Indianapolis, Ind.	174	148	144	155.3	0.023	0.036	0.021	0.027
Los Angeles, Calif.	186	151	119	152.0	0.055	0.041	0.031	0.042
Milwaukee, Wis.	155	146	150	150.3	0.029	0.023	0.011	0.021
New Orleans, La.	91	89	89	89.7	0.025	0.022	0.034	0.027
Newark, N.J.	113	113	103	109.7	0.057	0.084	0.066	0.069
Oklahoma City, Okla.	71	83	87	80.3	0.013	0.014	0.003	0.010
Omaha, Nebr.	139	101	128	122.7	0.018	0.013	0.005	0.012
Philadelphia, Penn.	162	166	157	161.7	0.082	0.074	0.077	0.078
Phoenix, Ariz.	240	214	158	204.0	0.038	0.019	0.011	0.023
Pittsburgh, Penn.	166	179	156	167.0	0.042	0.028	0.031	0.034
Saint Louis, Mo.	175	134	137	148.7	0.018	0.013	0.012	0.014
San Francisco, Calif.	81	68	76	75.0	0.029	0.023	0.023	0.025
Seattle, Wash.	125	68	82	91.7	0.079	0.059	0.037	0.058
Tacoma, Wash.	111	96	81	96.0	0.051	0.038	–	0.045
Washington, D.C.	111	98	90	99.7	0.049	0.040	0.021	0.037
AVERAGE	154.5	137.4	124.5	139.0	0.047	0.036	0.026	0.037

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[a] Data from McMullen[390] and Tabor (personal communication).

In a general sense, the presence of a large quantity of suspended particles appears to be accompanied by a high concentration of nickel. However, of the group of cities with the highest concentrations of the suspended particles (Chattanooga, 199 $\mu g/m^3$; Charleston, West Virginia, 238 $\mu g/m^3$; East Chicago, Indiana, 202 $\mu g/m^3$; Phoenix, Arizona, 204 $\mu g/m^3$; and El Paso, Texas, 190 $\mu g/m^3$), only East Chicago conforms to this general rule. The other four cities have nickel concentrations near or below the average.

It is possible that such averages oversimplify the true picture. As one example, McMullen's plot[390] of nickel concentration against suspended-particle concentration for Seattle (Figure 2-5) is shown to display how wide a variation may be concealed by averaging. Figure 2-6 gives a similar plot[390] for the nonurban area of Parke County, Indiana. A large difference in scatter of the points is evident between these two graphs, suggesting that the tabular method of reporting (Table 2-14) is not adequate; it might be necessary to relate the sampling procedure temporally with factors in local nickel emission. McMullen did conclude that, in general, the nickel concentration in the air was related to the total particle concentration in the air, increasing or decreasing as the particle concentration changed.

The National Air Surveillance Networks has reported[657] similar data based on air samples collected between 1960 and 1965 and issued in a 1966 edition. The concentrations of particles collected are summarized below:

	Suspended Particles, $\mu g/m^3$	
Sources	arithmetic mean	maximal station average
217 urban sites	102	254
30 nonurban sites	38	79

The data for airborne nickel concentrations in this report[657] have been augmented by more recent data from the Division of Atmospheric Surveillance of NASN. The combined data have been compiled in Appendix A, representing results obtained in 213 urban and 47 nonurban localities. The following overall averages are of particular interest:

	Nickel Concentration, $\mu g/m^3$	
	urban	nonurban
Averages for all quarters	0.021	0.006
Averages for fall and winter	0.025	0.006
Averages for spring and summer	0.017	0.006

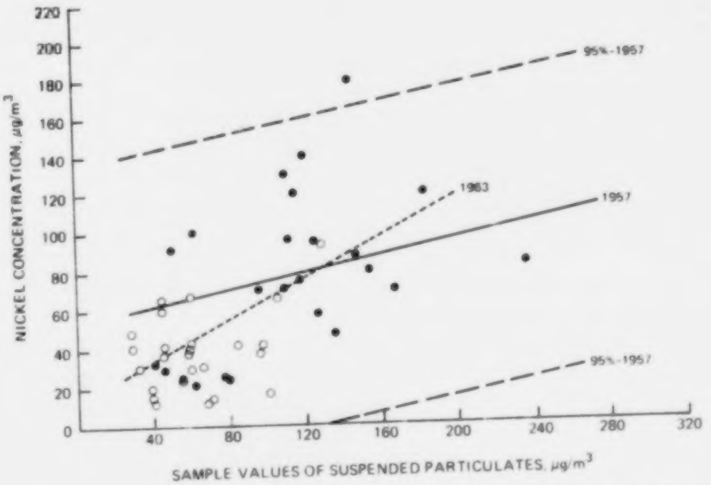

FIGURE 2-5 Suspended particles versus nickel concentration in air samples taken in Seattle, Washington. Dots, 1957; circles, 1963; 95% lines represent confidence limits. Derived from McMullen.[399]

Two conclusions may be drawn: (1) there is a definite difference in airborne nickel concentration between urban and nonurban areas; and (2) more nickel is present in urban atmospheres in the cold quarters than in the warm quarters, but no such difference exists in nonurban atmospheres.

The seasonal effect has been noted by Schroeder[525] in examining the data of Tabor and Warren[629] and of the National Air Surveillance Networks.[657] Schroeder determined the mean nickel concentration in the

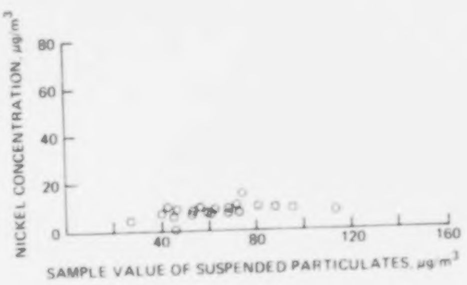

FIGURE 2-6 Suspended particles versus nickel concentration in air samples taken in Parke County, Indiana (nonurban), 1964. Derived from McMullen.[399]

samples from 10 of the more polluted (by nickel) cities; it was 0.044 $\mu g/m^3$ for the colder months and 0.026 $\mu g/m^3$ for the warmer months. He attributed this difference to nickel emission from coal and fuel oil burned for space heating.

The averages quoted above from Appendix A would undoubtedly have displayed a greater seasonal variation if all sampling data from southern cities had been deleted on the grounds that they were not influenced by space-heating emission; this separation was not made, simply because of doubt as to where the geographic dividing line should be drawn.

The seasonal effect was studied in further detail in measurements of airborne nickel particulate concentrations in New York City,[309] which showed a significant correlation between nickel content and such variables as air temperature, atmospheric stability, and vanadium content. The relation between nickel and vanadium content was said to demonstrate the usefulness of the two elements as tracers for particles from specific oil-burning sources. Three sampling locations were used: lower Manhattan, mid-Manhattan, and the Bronx at Sedgwick Avenue and Major Deegan Expressway. The results from two sites are shown below, with additional data secured from the nonurban area of Tuxedo, New York; these three were operated for the full 1968 calendar year. The reported limit of detection for nickel in New York City was 0.006 $\mu g/m^3$.[309]

	Concentration, $\mu g/m^3$		
	lower Manhattan	Bronx	Tuxedo
Particles, annual mean	125	113	36.7
Nickel, annual mean	0.16	0.15	0.068
Nickel, annual range	0.07–0.21	0.06–0.25	0.01–0.16

A detailed study of nickel in relation to quantity of particles, cold versus warm months, wind velocity, etc., was made. The researchers concluded that:

- there was an inverse correlation of particles and nickel (and vanadium) with temperature;
- there was a direct correlation of particles and nickel (and vanadium) with atmospheric stability;
- there were intercorrelations of particles with nickel (and vanadium); and

- the increased nickel concentrations in the cold months were caused by emission from the combustion of coal and fuel oil for space heating.

Volchok and Bogen[677] sampled the total trace-metal particulate fallout in New York City monthly from December 1969 to March 1970 and from August to December 1970 and the trace metals in precipitation for the 4 months, September–December 1970. Their limited work to date does not provide a basis for conclusive interpretation, but their data (Table 2-15) do suggest a seasonal variation in the concentration of nickel in the atmosphere, thus concurring with the work of Kneip *et al.*[309]

A somewhat more restricted study was done by Lee *et al.*,[331] who took samples in 1967 for 10 days on a 24-h/day basis in downtown Cincinnati, Ohio, and simultaneously in the Indian Creek Wildlife Preserve near Fayetteville, Ohio. Their results are tabulated below:

Location	Nickel Concentration, μg/m³		
	maximum	minimum	average
Cincinnati	0.06	<0.01	0.02
Indian Creek	0.03	<0.01	0.01

Whether the analyses could have been determined to additional significant figures is not certain, but the values reported suggest a less precise method of analysis than was used by McMullen[390] or the National Air Surveillance Networks.[657] The 2:1 urban:nonurban ratio is also considerably below the 4.8:1 ratio that applies to the NASN data.

TABLE 2-15 Nickel Fallout, New York City, 1970[a]

Month	Fallout, μg/cm²[b]
Dec.	2.79
Jan.	1.16
Feb.	1.35
Mar.	1.39
Aug.	0.53
Sept.	0.74
Oct.	0.63
Nov.	0.55
Dec.	1.63

[a] Derived from Volchok and Bogen.[677]
[b] Area of collector, 761 cm².

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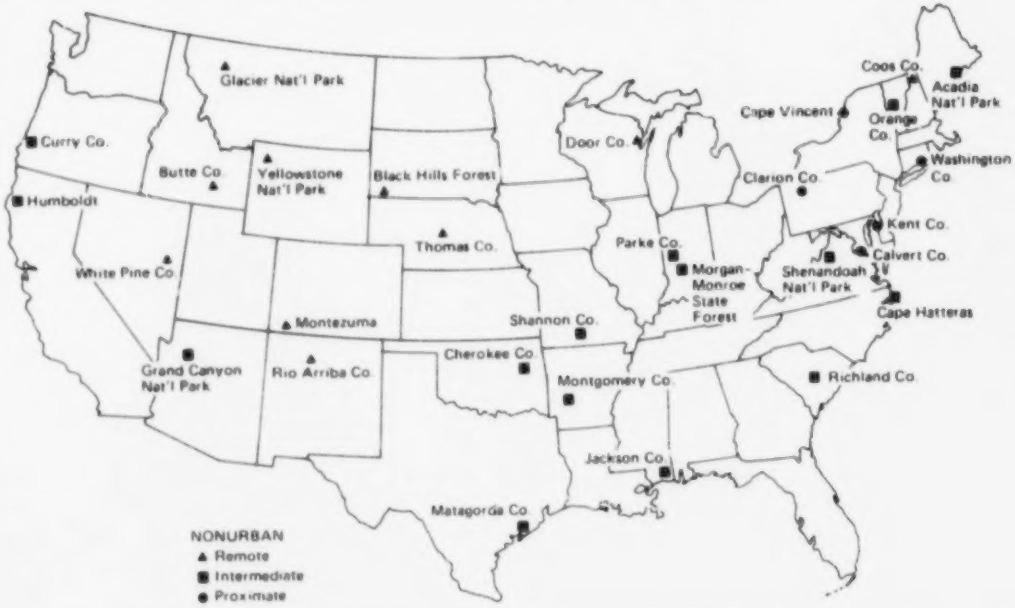


FIGURE 2-7 Distribution of air sampling stations in the continental United States. Data from McMullen *et al.*[391]

An air-sampling survey was performed by McMullen *et al.*[391] in 1966–1967, involving data from 217 urban and 30 nonurban stations scattered across the United States. The results are summarized below (the three types of nonurban stations are identified in Figure 2-7).

	Ambient-Air Concentrations, µg/m³			
	urban stations (217)	proximate (5)	intermediate (15)	remote (10)
Particles	102.0	45.0	40.0	21.0
Nickel	0.017	0.008	0.004	0.002

For purposes of appraisal, a comparison of the air-sampling data discussed in the preceding paragraphs is presented below.

	Comparative Nickel Concentrations, µg/m³	
	urban	nonurban
Table 2-14 (30 cities)	0.026–0.045	—
Appendix A (213 cities, 47 nonurban stations)	0.021	0.006
Lee *et al.*[331] (Cincinnati vs. Indian Creek)	0.02	0.01
Kneip *et al.*[300] (NYC vs. Tuxedo)	0.15–0.16	0.068
National Air Surveillance Networks[657] (217 cities, 30 nonurban stations)	0.017	0.002–0.008
Possible averages (excluding Kneip)	0.023	0.007

The values for New York City are conspicuously higher than the rest—a result that is perhaps understandable for a city of that size. The value for the nonurban location of Tuxedo, however, seems higher than is reasonable, suggesting that there may be a bias in the analytic methods used. The results in McMullen *et al.*[391] and the National Air Surveillance Networks[657] conform to a common magnitude, but probably represent the same analysts in each case. It does seem out of line, however, that, in view of the large number of stations sampled, McMullen and colleagues[390,391] should show a 2:1 ratio. This situation is further evidence of the need of the program for standardization of air-pollution measurement methods that is currently being undertaken by Committee D-22 of the American Society for Testing and Materials as "Project Threshold" for the U.S. air-pollution control agencies.[487] Examination of values from individual cities listed in Appendix A lends emphasis to this need. For example, the nickel concentrations for three particular cities do not compare well with each other (Bakersfield, California, 0.31 µg/m³; Rockford, Illinois, 0.009 µg/m³; and Birmingham, Alabama,

TABLE 2-16 Studies of Nickel Content of Individual Foods[a]

Authors	Dates	Items Covered	Source of Item	Analytic Method
Frei	1968	Oats	Canada	Thin-layer chromatography
Gabovich *et al.*	1964	Flour, vegetables, meat, fish, milk, milk products	USSR	Emission spectroscopy
Karetnikov *et al*	1966	Pine nuts	USSR (East Siberia)	Colorimetry
Karvánek *et al.*	1967	Margarine	Czechoslovakia	Photometry
Karvánek *et al.*	1966	Spinach	10 European and American varieties planted in Czechoslovakia	Photometry
Karvánek	1964	20 foods	Czechoslovakia (in part imported from other countries)	Colorimetry
Kirchgessner	1956–1959	Cows' milk	Germany	Colorimetry
Los' *et al.*	1966	Corn, peas	USSR	Photocolorimetry
Monier-Williams	1950	Oil, beer, milk	?	(Literature values)
Poljakova *et al.*	1968	Cereal, flour, bread, vegetables, cows' milk	USSR	Chromatography
Schroeder *et al.*	1962	About 90 foods	United States	Microchemistry
Taktakishvili	1963	About 30 foods	USSR	Colorimetry

[a] Derived from Schlettwein-Gsell and Mommsen-Straub.[522]

0.010 μg/m^3) and compare even less well with those of two nonurban samples (Acadia National Park, Maine, 0.013 μg/m^3; and Jackson County, Mississippi, 0.009 μg/m^3). Standardized analytic procedures are obviously urgently needed.

SUMMARY

Granting that some lack of agreement in results is to be expected, it is still evident that there is an appreciable amount of nickel in the air, independently of metallurgic processing, particularly in urban areas. Three sources have been suspected: exhausts of automobiles and trucks, burning of fuel oil for space heating, and burning of coal and oil for power generation. Nickel may be inhaled by urban residents at about 2–14 μg/day, depending on time and location (see Chapter 3).

Food

ENTRY OF NICKEL INTO THE FOOD SUPPLY

Man's exposure to nickel in food derives from the natural occurrence of nickel in food ingredients and from man-made sources, such as alloys, food-processing equipment, and fungicides, which may increase the amount of nickel in food substances beyond that naturally present. Most of the available data on nickel content of individual foods have been summarized by Schlettwein-Gsell and Mommsen-Straub.[522] Table 2-16 lists the kinds of data available, including methods used for analysis. Detailed consideration of the methods used is required in evaluating their suitability for specific analyses and their reliability.

With the exception of some preliminary studies in plants, nothing is known about the chemical form of nickel in foods.[640] Detailed information of this type needs to be developed for consideration of possible differences in bioavailability and biotoxicity of nickel in foods. However, the available information indicates that the concentrations of nickel in foods are low and do not pose any toxicity problem.

ROUTES OF NICKEL INTO THE FOOD CHAIN

The presence of nickel in soil and water results in its being incorporated into all organisms by being passed from primary producers—e.g., zooplankton, phytoplankton, and plants—to primary and secondary consumers. Of chief importance in the entry of nickel into these food chains are geochemical factors involved in releasing nickel in a soluble form into the environment; information on global contamination of air, water, and soil by human activities; and biologic factors involved in the accumulation and metabolism of nickel by plants and animals.

NICKEL IN PLANTS

The occurrence of nickel in plants and soils has been reviewed by Vanselow.[669] Soils normally contain nickel at 5–500 ppm, although soils formed from serpentine rock may contain as much as 5,000 ppm. Table 2-17 shows soil-to-plant movement of nickel.

Most investigations of nickel in soil and its effects on plant growth have resulted from observations of poor growth in soils derived from basic rocks or serpentine. Excess nickel produces chlorosis, whose overall effect resembles iron deficiency. The total nickel content of soils is not a good measure of availability. The nickel content of plants appears to be closely correlated with exchangeable nickel in the soils. In peaty serpentine soils,[349] a large part of the nickel present is in a complex with organic matter, and its uptake by plants is reduced by raising the soil pH. Chelation is correlated with the organic carbon content of soil.[105] Halstead *et al.*[217] attempted to define critical concentrations of of nickel in plants and soils that were adverse for crop yield. When the nickel concentration reached 60 ppm in oat grain (500 ppm in soil), 28 ppm in oat straw, and 44 ppm in alfalfa, there was decreased yield.

The nickel concentration in most natural vegetation is 0.05–5 μg/g (or parts per million) on a dry-weight basis. Various grasses, including field-grown oats, contained 4–134 μg/g of dry tissue.[506] Nickel concentrations in plant materials commonly used as foods are listed in Tables 2-18 and 2-19. Plant products may show significant area or varietal differences in nickel content. For example, the nickel contents of three wheats—common hard, common soft, and durum—were 0.47 ± 0.08 μg/g, 0.31 ± 0.08 μg/g, and 0.29 ± 0.14 μg/g, respectively.[727]

Although nickel concentrations above 50 ppm in plants are usually toxic, some plants, particularly those endemic to serpentine, may contain much higher concentrations; e.g., some forget-me-nots and some rice flowers contained 6,100 and 5,500 ppm (expressed as ppm of ash). Some alyssum contained 4,000 ppm in leaves and 250 ppm in seeds (dry tissue).[409,539]

In plants, nickel appears to be translocated in the xylem in two forms, the total amount of each depending on the total nickel translocated.[640] Studies of nickel absorbed by plant roots and translocated in xylem exudates, followed by electrophoresis of the exudate, showed that at physiologic nickel content ($<3\ \mu M$) in the xylem, it was translocated mainly as a negatively charged molecule. The anodic complex of nickel appears to

TABLE 2-17 Nickel in Grains[a]

Grain or Grain Product	Nickel Concentration, ppm
	Fresh weight
Wheat, winter, seed	0.16
Wheat, Japanese	0
Wheat, Japanese	0
Wheat flour, Japanese	0
Wheat flour, all-purpose	0.54
Wheat flour, all-purpose	0.30
Wheat, crushed, Vermont	0.75
Bread, whole-wheat, stone-ground	1.33
Wheatena	0
Wheaties	3.00
All-bran cereal	0.74
Grapenuts cereal	0.13
Buckwheat, seed	6.45
Rye, seed	2.70
Oats, seed	2.60
Oats, seed	1.71
Oats, precooked, quick	2.35
Corn, frozen, fresh	0.70
Corn meal, New Hampshire	0
Corn oil	0
Rice, Japanese, polished	0.50
Rice, Japanese, unpolished	1.80
Rice, Japanese, polished (204 samples)	0.65
Rice, American, polished	0.47
Rice, puffed	0.30
Rye flour	0.23
Rye bread	0.21
	Dry weight
Corn, grain, mature	0.14
Oats, grain, mature	0.45
Oats, leaves, June	16-51
Oats, leaves, mature	7.00
Rice, polished	0.02
Buckwheat, seeds	1.34
Barley	4-6
Wheat, mature grain	0.35-35

[a] Data from Schroeder *et al.*,[528] Schlettwein-Gsell and Mommsen-Straub,[521] and Vanselow.[669]

be very stable. The nature of the chelate component has not been established. The chelate form of nickel has been detected in five species of plants so far studied (tomato, cucumber, corn, carrot, and peanut). It is not known whether the chelate is the common form of nickel in plant materials or whether the formation of this complex in any way alters the bioavailability or biotoxicity of nickel.

TABLE 2-18 Nickel in Vegetables and Fruits[a]

Vegetable or Fruit	Nickel Concentration, ppm
	Fresh weight
Potato, raw	0.56
Peas, fresh, frozen	0.30
Peas, canned	0.46
Peas, split, dried	1.66
Beans, string, frozen	0.65
Beans, string, canned	0.17
Beans, navy, dried	1.59
Beans, yellow-eye, dried	0.69
Beans, red kidney, dried	2.59
Spinach, fresh	0.35
Celery, fresh	0.37
Beet greens	1.94
Swiss chard, organic	0.71
Escarole, fresh	0.27
Chicory, fresh	0.55
Lettuce, garden, organic	1.14
Lettuce, head	0.14
Kale, organic	1.12
Kohlrabi, leaves, organic	0.47
Cabbage, white	0.32
Cabbage, white	0.14
Cabbage, red	0.24
Cauliflower leaves	0.19
Broccoli, fresh, frozen	0.33
Tomato, fresh	0.02
Tomato juice, canned	0.05
Apple, raw	0.0
Apple, raw	0.08
Banana	0.34
Pear	0.20
	Dry weight
Spinach	2.4
Squash	4.6
Tomato	0.01–0.15
Cabbage	3.30
Carrot, root	0.30
Carrot, leaves	1.80
Cress, water, tops	0.50
Cress, water, leaves	0.13
Mushroom	3.5
Pea	2.00
Potato	0.08–0.37
Onion	0.16
Lettuce	1.51
Cabbage	3.3
Lentils	1.61

TABLE 2-18 *Continued*

Vegetable or Fruit	Nickel Concentration, ppm
Peas	2.25
Haricot beans	0.59
Tomato	0.154
Orange	0.16
Apricot	0.64
Plum	0.90
Pear	0.90
Fig	1.20

[a] Data from Schroeder *et al.*,[528] Vanselow,[669] and Bertrand and Mokragnatz.[47]

TABLE 2-19 Nickel in Seafood[a]

Seafood	Nickel Concentration, ppm fresh wt
Oysters, fresh	1.50
Mollusks (Puget Sound)	0.74
Clams, fresh	0.58
Shellfish (Japanese)	0.14
Scallops, fresh-frozen	0.04
Lobster, claw meat	0.66
Shrimp, fresh-frozen	0.03
Crabmeat, canned	0.03
Anchovies, canned	0.72
Sardines, canned	0.21
Haddock, frozen	0.05
Swordfish, frozen	0.02
Salmon flesh	1.70
Dressed-fish samples	
Whitefish, Moose Lake	0.2
Northern pike, Moose Lake	0.2
Whitefish, Lake Ontario	0.2
Northern pike, Lac St. Pierre	0.2
Northern pike, Lake Erie	0.2
Smelt, Lake Erie	0.2
Yellow perch, Lake Erie	0.2

[a] Data from Bligh,[51] Laevastu and Thompson,[322] Nagahiro *et al.*,[420] and Schroeder *et al.*[528]

Contamination of roadside soil with nickel and later increase in nickel content of grasses has been reported by Lagerwerff and Specht.[323] The increase in nickel content of grass ranged from 1.3 to 3.8 ppm (dry wt), depending on distance from the highway. The roadside distribution of nickel was considered to have been derived from motor-vehicle fuel or atmospheric abrasion of nickel-containing automobile parts. Inasmuch as automotive tires and brake linings contain nickel, abrasion of these components may contribute nickel to the environment. Little information is available on this point.

The presence of nickel in superphosphate fertilizers may result in increased concentrations of nickel in plants.

Nickel salts display fungicidal activity against plant pathogens, and their use as fungicidal sprays has been suggested, but not approved. Such use could lead to increased nickel content of treated crops. Stewart and Ross[567] have shown that sprayed nickel salts are translocated in the plant. The mode of entry from the leaves is not known. In studies in which mature Cortland apple trees were sprayed to runoff with an aqueous solution of nickel chloride containing nickel at 37 ppm, initial deposits of nickel in fruit were 67–71 μg/10 apples, and at harvest time, 125–199 μg/10 apples. The peel:pulp ratio at harvest averaged 0.49:1–0.75:1.

NICKEL IN FISH AND SEAFOODS

Measurements of nickel in marine organisms have been reported by Laevastu and Thompson,[322] Pringle *et al.*,[486] Timourian and Watchmaker,[641] Nagahiro *et al.*,[424] and Stevenson and Ufret.[566] The concentration of nickel by algae, which obtain all their mineral nutrients from the ocean, has been calculated by Bowen.[55] The affinity for nickel of plankton and brown algae is lower than that for other transition metals. The relative order for plankton is zinc > lead > copper > manganese > cobalt > nickel > cadmium, and for brown algae is lead > manganese > zinc > copper > cadmium > cobalt > nickel. In the case of plankton, the concentration factor was 1,700, and for brown algae, 140–500. Timourian and Watchmaker[641] have demonstrated that there is active uptake of nickel by fertilized eggs and embryos of the sea within *Lytechinus pictus*.

Nickel contents reported for seafood are listed in Table 2-19. The studies of Nagahiro *et al.*[424] and Laevastu and Thompson[322] suggest that food-chain concentration of nickel occurs. Nagahiro *et al.*[424] measured nickel in flesh and shells of three Japanese shellfish (*Meretrix meretrix*, *Paphia philippinarum*, and *Corbicula leana*), and they found that the ranges of nickel contents in dry flesh and shell were 0.5–2.2 ppm and 0.04–0.10 ppm, respectively. The enrichment factors of nickel in dry flesh and shell were 300–800 and 30–40, respectively. Laevastu and Thompson[322] found that the flesh of West Coast salmon (*Oncorhynchus kisutch*) contained about three times the concentration of nickel as that found in other fish and about twice that of the mollusks that they examined. Nomoto *et al.*[448] found that the nickel concentration in lobster serum was greater than the nickel concentrations in serum of several mammalian species.

NICKEL IN ANIMAL FEEDS, TISSUES, ORGANS, AND PRODUCTS

The presence of nickel in ruminant ration has been reviewed by O'Dell and Miller.[451] O'Dell *et al.*[454] studied the effect of dietary nickel on excretion and nickel content of tissues in male calves. When diets contained up to 250 ppm for an 8-week period, there was no increase in the nickel content of liver, kidney, or other tissues studied, with the exception of the lung. However, at 1,000 ppm there was a significant increase in the nickel content of many tissues. In another study, feeding cows diets supplemented with nickel salts up to 1,750 ppm did not result in the presence of any detectable nickel in their milk.[452]

Cattle appear to have a mechanism to prevent accumulation of nickel from that normally encountered in the diet. Data of this type may not be available for other farm animals. However, it seems likely that other mammalian species have a similar mechanism to control nickel content of tissues.

The concentrations of nickel in meats, animal tissues, and animal products are listed in Table 2-20. Nickel contents of various liquids are listed in Table 2-21. Nickel concentrations in condiments are listed in Table 2-22.

TABLE 2-20 Nickel in Meats and Animal Food[a]

Item	Nickel Concentration, ppm fresh wt
Pork chop	0.02
Beef, marrow	0.22
Gelatin	4.50
Egg, whole	0.03

[a] Data from Schroeder *et al.*[illegible]

TABLE 2-21 Nickel in Liquids[a]

Fluid	Nickel Concentration, ppm fresh wt
Milk, evaporated	0.03
Tea, orange pekoe	7.60
Cocoa	5.00
Ginger ale	0.01
Cider	0.55
Cider vinegar	0.22
Beer, canned	0.01
Mineral water, bottled, Arkansas	0.01
Coffee, green "Robusta"	0.26
Coffee, green "Colombian"	0.10
Tea, Chinese	0.51-0.65
Wine, white, Slovakian	0.09
Wine, red, Moravian	0.12

[a] Data from Schroeder *et al.*[528] and Karvánek.[288]

NICKEL ABSORBED BY FOOD DURING PROCESSING

The use of nickel-containing alloys in food-processing equipment provides a potential source for introduction of nickel into the food supply. Monier-Williams[415] has reviewed available data on the corrosion of nickel-alloy vessels during food processing. Most of the reports indicate that some nickel will be dissolved in the food, the amount depending on the pH of the food and the composition of the alloy. Titus *et al.*[648] measured the amount of nickel, chromium, and iron entering various kinds of food cooked in contact with strips of alloys containing vari-

TABLE 2-22 Nickel in Condiments[a]

Condiment	Nickel Concentration, ppm fresh wt
Salt, table	0.35
Pepper, black	3.93
Baking powder	13.40
Sugar, cane	0.03
Yeast, dry active	0.48
Cinnamon	0.74
Nutmeg	1.17
Allspice	0.79
Bay leaves	0.88
Cloves, whole	0.10

[a] Data from Schroeder *et al.*[528]

ous amounts of these components. The average amounts of metal entering foods of various kinds cooked for 1 h are shown in Table 2-23.

It is important, however, to consider the grade of stainless steel to be used and whether it has been properly heat-treated. Lack of corrosion resistance in cooking vessels has been reported in a recent issue of *Consumer Bulletin*,[435] which stated that a solution at the pH of acid foods leached nickel at more than 400 ppm from some stainless-steel pans. With the increasing use of stainless steel for food-processing equipment, there is a need to evaluate the corrosion resistance for particular processes, so that excessive contamination of food does not occur. In general, experience has indicated that the stainless steels most likely to be used with foods or by the food-producing industry dissolve only very minute amounts of metal, even under extreme conditions. Lehman[332] has concluded that "these trace quantities have no pharmacologic significance" and that alloys are safe.

The amount of nickel in the food supply may be increased by such processes as the milling of flour. Zook *et al.*[727] measured the concentrations of eight trace elements, including nickel, in wheat or wheat blends (commercially prepared flours from these wheats). The concentration of nickel (as well as those of tin, cadmium, and chromium) was higher in cake and crackers than in the flour from which they were made, as shown in Table 2-24.

Milling byproducts and other ingredients of the wheat-flour products studied were not analyzed for minerals; hence, the source of the increase in nickel content has not been established, although the most probable source of this increased content was the fat used.

The catalysts used in commercial hydrogenation of fats usually consist of nickel, although other metals in small amounts, such as copper

TABLE 2-23 Average Dissolution of Elements from Standard Grades of Stainless Steel by Various Foods[a]

	Dissolution, ppb[b]		
Grade of Stainless Steel	Iron	Chromium	Nickel
AISI 316 - strips[c]	3.04	0.75	0.20
AISI 302 - strips[c]	3.37	0.19	0.18
AISI 302 - container[d]	2.81	0.36	0.13

[a] Derived from Titus *et al.*[660]

[b] 400 g of food cooked 1 h in each case.

[c] 4 dm² of alloy in contact with food.

[d] Food cooked directly in stainless-steel container; surface exposed to liquid was 4 dm².

TABLE 2-24 Nickel in Wheat, Wheat Blends, and Wheat Products

Product	Nickel Concentration, ppm
Cracker	
straight-grade	0.20
air-classified	0.14
Cake	
soft patent	0.15
air-classified	0.22
Wheat, common hard	0.47 ± 0.08
flour, Baker's patent	0.15 ± 0.05
bread, sponge-dough	0.73 ± 0.21
bread, continuous mix	0.72 ± 0.25
Wheat, common soft	0.31 ± 0.08
flour, soft patent (cake)	0.18 ± 0.07
cake	0.82 ± 0.16
flour, straight-grade	0.18 ± 0.03
cracker	0.81 ± 0.23
flour, cutoff (cracker)	0.17 ± 0.07
cracker	0.85 ± 0.39
Wheat, durum	0.29 ± 0.14
Semolina	0.18 ± 0.04
macaroni	0.15 ± 0.05
Cereal-to-be-cooked	0.28 ± 0.07
Shredded wheat	0.64 ± 0.20
Wheat flakes	0.71 ± 0.15
Bread, whole wheat	0.82 ± 0.21
Bread, white	
conventional dough	0.49 ± 0.04
continuous-mix	0.65 ± 0.13
Rolls, hamburger	0.52 ± 0.04
Doughnuts, cake	0.41 ± 0.09
Biscuit mix	0.72 ± 0.09
Flour, all-purpose	0.20 ± 0.06

and aluminum, may be present as "promoters." Hydrogenation is usually carried out with powdered metals or finely divided metals supported on inert materials, such as diatomaceous earths. In addition, Raney catalyst, a 1:1 alloy of nickel and aluminum, is used extensively for hydrogenation of fats and oils. The concentration of catalysts is an important factor in determining the rate of hydrogenation of the oil. It may range from 0.012% to 0.25% nickel. Details on the relation between amount of nickel catalyst used, reuse of nickel catalyst, and amount of nickel in final product do not appear to be available. Dry-reduced catalysts can usually be removed from oil by filtration; however, the use of "wet-reduced" catalysts (i.e., when the catalyst is a nickel salt, such as nickel formate, which decomposes to metallic nickel in the heated oil during the hydrogenation process) requires addition of bleaching earth to the oil for complete removal of the catalyst. Soybean oil, a major food fat, is commonly hydrogenated to improve its oxidative stability, flavor, and physical properties. Some nickel remains after careful purification. Beal and Sohns[40] reported on methods for removal of metallic ions, including nickel, in the processing of the oil. The partially hydrogenated soybean oil initially contained nickel at 0.22–0.46 ppm. The nickel content was reduced to 0.02–0.05 ppm, using the methods described. However, these methods may not always be used in the preparation of commercially hydrogenated fats, inasmuch as samples of shortening often contain nickel at 0.2–6.0 ppm (personal communication from large domestic manufacturer, based on analysis of 15 samples). However, the nickel content of hydrogenated oils is generally less than 0.1 ppm.

3

Nickel Metabolism in Man and Animals

ROUTES OF INTAKE AND ABSORPTION

There are four routes of entry of nickel into the body: *oral intake*, i.e., in food and drinking water, both of which may include some nickel derived from cooking and eating utensils; *inhalation*, i.e., from the atmosphere and tobacco smoke; *percutaneous absorption*, a route that is probably of negligible quantitative significance, but is clinically important in the pathogenesis of nickel dermatitis (see Chapter 5); and *parenteral administration*, i.e., in medications and metallic devices and prostheses (see Chapter 6).

Schroeder *et al.*[528] calculated the usual oral intake of nickel by American adults at 300–600 μg/day. Nickel ingestion may vary widely. Schroeder and co-workers calculated that a person who ingests a 2,300-cal diet containing 100 g of protein, 250 g of carbohydrate, and 100 g of fat and who consumes meat, milk, fruit, refined white bread, wheatena, butter, and corn oil would take in 3–10 μg of nickel per day. At the other extreme, a diet that has the same caloric value and the same proportions of protein, carbohydrate, and fat might contain 700–900 μg of nickel per day, if the person consumes oysters, meat, milk, eggs, oats, whole-wheat or rye bread, some vegetables, potatoes, and legumes, with little added fat. The wide range of oral intake of nickel may also result from variable ingestion of beverages—such as tea, coffee, beer, and red wine—that contain more than 100 μg of nickel per 100 g.[522] Primarily on the basis of the data of Schroeder *et al.*,[528] Louria and co-workers[347] estimated the average oral intake of nickel in American adults at 500 μg/day. Taktakishvili[631] reported that the average oral intake of nickel in Russian adults is 300 μg/day. Tedeschi and Sunderman[636] measured nickel ingestion in dogs that were permitted free access to Purina Dog Chow and found that it averaged 373 μg/day. Sunderman *et al.*[621] reported that a patient who was given a liquid diet (Metrecal) *ad libitum* ingested an average of 240 μg of nickel per day. Metal cooking pots and eating utensils that are made of nickel-containing alloys can contribute to the oral ingestion of nickel.[648]

Most of the nickel that is ingested in food remains unabsorbed within the gastrointestinal tract and is excreted in the feces. Elakhovskaya[143] reported that nickel given orally to rats as nickel chloride in the drinking water was excreted mainly in the feces. Tedeschi and Sunderman[636] reported that dogs excreted 90% of ingested nickel in the feces and only 10% in the urine. Horak and Sunderman[254] found that fecal excretion of nickel by healthy human subjects was an average of 100 times greater than urinary excretion. Schroeder *et al.*[528] stated that there appears to be a mechanism that limits the intestinal absorption of nickel in mammals, despite the relatively large amount of nickel present in their food.

Data on the concentrations of nickel in the atmosphere of various rural and urban areas are summarized in Chapter 2, and data on the nickel content of cigarettes and other tobacco products are summarized in Chapter 6. There is wide variation in the average concentrations of nickel in urban atmospheres.[525,526] Of urban areas of the United States that were surveyed during 1964 and 1966, the cleanest with respect to atmospheric nickel were Boise, Idaho; Albuquerque, New Mexico; and Moorhead, Minnesota. No nickel was detected in those three areas in the 1966 survey. In comparison, the cities with the highest atmospheric concentrations of nickel were New York City (1966 average, 0.118 μg/m^3 of air) and East Chicago, Indiana (1964 average, 0.69 μg/m^3). On the basis of these measurements, Schroeder[525,526] estimated the daily inhalation of nickel by residents of New York City and East Chicago, assuming that 20 m^3 of air (24.1 kg) is inhaled daily and that all inhaled nickel is retained in the body. Schroeder calculated that during 1966 an adult resident of New York City could have inhaled 2.36 μg of nickel per day and that during 1964 an adult resident of East Chicago could have inhaled a maximum of 13.8 μg of nickel per day.

Making similar assumptions, Sunderman and Sunderman[595] calculated that a cigarette smoker would inhale a maximum of 14.8 μg of nickel per day from 40 cigarettes. As Schroeder has pointed out,[525,526] the actual retention of inhaled nickel within the body is probably only 75% of the calculated intake; roughly 25% would be expired, depending on the particle size distribution. Approximately 50% of inhaled nickel dust might be expected to be deposited on bronchial mucosa and swept upward in mucus to be swallowed, and 25% would be expected to be deposited in the pulmonary parenchyma. In the case of inhalation of a gaseous nickel compound, such as nickel carbonyl, a much larger proportion of inhaled nickel would reach the pulmonary parenchyma.[292]

Natusch *et al.*[430] have measured the content of nickel in fly ash released from coal-fired power plants, and they have observed that nickel is concentrated in the smallest respirable particles. Thus, the nickel content of fly-ash dusts with a particle diameter of 4.7 μm averaged 0.4 mg of nickel per gram. In comparison, the nickel content of fly-ash dusts with particle diameters ranging from 1.1 to 2.1 μm averaged 1.6 mg of nickel per gram (Table 3-1). Moreover, the sulfur content was significantly greater in the smaller particles than in the larger particles. Natusch *et al.*[430] suggested that, during the combustion of coal, nickel may have access to the vapor phase as nickel sulfides or nickel carbonyl, and that these vapors may later recondense or decompose, with preferential adsorption of nickel onto the large available surface area per unit mass that is provided by the small smoke particles. Their investigation demonstrates that the particles of fly ash that are most likely to reach the lungs contain the highest concentrations of nickel. Moreover, computations of inhaled nickel that are based on analyses of undifferentiated dusts obtained with particle precipitators may grossly underestimate the amount of nickel that actually reaches the lungs.

The metabolism of nickel that enters the body by the pulmonary route is similar to that of nickel compounds that are administered paren-

TABLE 3-1 Nickel in Coal Fly Ash (Analyses by Atomic Absorption)[a]

Particle Diameter, μm	Nickel Concentration, μg/g	Sulfur Concentration, wt %
>11.3	460	8.3
7.3–11.3	400	—
4.7–7.3	440	7.9
3.3–4.7	540	—
2.1–3.3	900	25.0
1.1–2.1	1,600	—
0.6–1.1	—	48.8

[a] Derived from Natusch *et al.*[430]

terally.[619] Inhaled nickel carbonyl is excreted primarily in the urine and to a minor degree in the feces.[619,636] Kemka[297] has reported a correlation of atmospheric concentrations of nickel in a nickel smelting plant with the concentrations of nickel in the urine of exposed workmen.

CONCENTRATION AND PARTITION

Concentrations in Biologic Fluids, Hair, and Excreta

Tables 3-2 to 3-4 list the concentrations of nickel that have been found by various investigators in human serum, plasma, whole blood, and urine. The lower concentrations of nickel in biologic fluids observed by Nomoto and Sunderman[449] and McNeely *et al.*[392] result from the improved sensitivity and specificity of their method of analysis—atomic-absorption spectrometry. McNeely *et al.*[392] have shown that measurements of nickel in serum and urine can serve as biologic indexes of environmental exposure to nickel. They measured the nickel in serum and urine specimens from healthy, adult residents of Hartford, Connecticut, a city with relatively low environmental concentrations of nickel, and Sudbury, Ontario, Canada, the site of the largest open-pit nickel mines in North America. None of the subjects had occupational exposure to nickel. In the Hartford population, serum nickel concentrations averaged 2.6 ± 1.0 μg/liter, and urine nickel excretion averaged 2.5 ± 1.4 μg/day. In the Sudbury population, serum nickel concentrations averaged 4.6 ± 1.4 μg/liter, and urine nickel excretion averaged 7.9 ± 3.7 μg/day. These population means were significantly different ($p < 0.001$). The measurements by McNeely *et al.* provide the first direct evidence that measurements of nickel in serum and urine reflect environmental exposure to nickel. It must be emphasized that there is not yet any evidence that the environmental exposure to nickel in Sudbury, Ontario, is associated with adverse effects in man or animals.

Measurements of nickel concentrations in hair samples from healthy adults have been reported by Schroeder and Nason[532] and by Nechay and Sunderman.[431] In the study of Schroeder and Nason,[532] hair clippings of unspecified length were obtained from a barber shop. When the samples of hair had been washed with carbon tetrachloride, they were ashed in a muffle furnace, and the ash was dissolved in dilute hydrochloric acid. Direct measurements of nickel in the acid solutions were performed by atomic-absorption spectrometry. Schroeder and Nason reported that the nickel concentrations of hair samples from men were significantly lower than those of hair samples from women: the

TABLE 3-2 Nickel Concentrations in Human Serum and Plasma

Author	Method	Area	No. Subjects	Serum(S) or Plasma(P)	Nickel Concentration, μg/100 ml	
					Mean	Range
Cluett and Yoe[88]	Spectrophotometry	Virginia	1	P	1.2	–
Koch *et al.*[310]	Emission spectrography	New York	?	P	3.0	1.0–8.5
Monacelli *et al.*[412]	Emission spectrography	Virginia	12	P	4.0	1.0–6.0
Paixao and Yoe[458]	Emission spectrography	Virginia	39	P	2.3	0.0–18
Herring *et al.*[239]	Emission spectrography	Virginia	109	P	6.0	0.0–27
Gofman *et al.*[202]	Emission spectrography	California	39	S	–	0.0–18
Butt *et al.*[68]	Emission spectrography	California	48	S	5.3–6.2[a]	–
Zhernakhova[724]	Emission spectrography	Russia	154	S	5.5 ± 2.8 (male)	–
					2.2	0.1–7.3
Sunderman[604]	Spectrophotometry	Florida	23	S	2.2	0.1–7.3
Schaller *et al.*[521]	Atomic absorption	Germany	26	P	2.1	0.6–3.7
Mertz *et al.*[399]	Emission spectrography	Germany	59[b]	S	0.78	0.06–4.60
Howard (personal communication)	Emission spectrography	England	50	S	2.1	0.1–5.0
Nomoto and Sunderman[449]	Atomic absorption	Connecticut	40	S	0.26	0.11–0.46
Niedermeier *et al.*[430]	Emission spectrography	Alabama	105[c]	S	4.0	<1–25
McNeely *et al.*[392]	Atomic absorption	Connecticut	26	S	0.26	0.08–0.52
		Canada[d]	25	S	0.46	0.20–0.73
Pekarek and Hauer[471]	Atomic absorption	Washington, D.C.	20	S	1.5 ± 0.5	–
Nomoto[448]	Atomic absorption	Japan	23	S	0.21 ± 0.11	–

[a] Confidence limits of mean value; nickel not detected in 18 serum samples.
[b] Includes 25 healthy subjects and 34 patients.
[c] Nickel not detected in 57% of serum samples.
[d] Sudbury, Ontario.

TABLE 3-3 Nickel Concentrations in Human Whole Blood

Authors	Method	Area	No. Subjects	Nickel Concentration, μg/100 ml Mean	 Range
Cluett and Yoe[88]	Spectrophotometry	Virginia	8	4.1	2.5–6.7
Paixao and Yoe[418]	Emission spectrography	Virginia	40	3.6[a]	–
Imbus *et al.*[290]	Emission spectrography	[b]	153	4.2	0.9–9.8[c]
Butt *et al.*[86]	Emission spectrography	California	47	32.7	–
Schaller *et al.*[526]	Atomic absorption	Germany	63	2.7	0.6–7.0
Szadkowski *et al.*[627]	Atomic absorption	Germany	20	2.3 ± 0.7	–
Nomoto and Sunderman[449]	Atomic absorption	Connecticut	17	0.48	0.29–0.70
Delves *et al.*[119]	Atomic absorption	England	76[d]	2.2	–

[a] Calculated from values for plasma and red cells.

[b] Industrial workers from Ohio, New York, Florida, Colorado, and Oregon.

[c] 2.5–97.5 percentile.

[d] Children.

TABLE 3-4 Nickel Concentrations in Human Urine

Authors	Method	Area	No. Subjects	Nickel Concentrations, μg/100 ml[a] Mean	Range
Tompsett and Fitzpatrick[450]	Spectrophotometry	England	12	2.9	0.0–5.5
Kinkaid *et al.*[300]	Spectrophotometry	Pennsylvania	69	1.1	0.0–3.0
Perry and Perry[478]	Emission spectrography	Missouri	24	2.0	1.0–7.0
Morgan[417]	Spectrophotometry	Wales	?	4.0 ± 0.2	–
Imbus *et al.*[270]	Emission spectrography	[b]	154	1.0	0.1–2.5[c]
Sunderman[600]	Atomic absorption	Pennsylvania	17	1.8 (19.8)	0.4–3.1
Nomoto and Sunderman[388]	Atomic absorption	Connecticut	26	0.23 (2.4)	0.10–0.52 (1.0–5.6)
Lehnert *et al.*[334]	Atomic absorption	Germany	15	(9.3)	(5.7–12.7)
Kemka[297]	Spectrophotometry	Yugoslavia	10	2.7	1.4–6.3
McNeely *et al.*[362]	Atomic absorption	Connecticut	20	0.20 (2.5)	0.07–0.40 (0.05–6.0)
		Canada[d]	19	0.72	0.21–1.65

[a] Numbers in parentheses are concentrations in micrograms per day.
[b] Industrial workers from Ohio, New York, Florida, Colorado, and Oregon.
[c] 2.5–97.5 percentile.
[d] Sudbury, Ontario.

mean in 79 men was 0.97 μg/g (SEM = ± 0.15), and the mean in 25 women was 3.96 μg/g (SEM = ± 1.06)—a significant difference ($p < 0.001$). Schroeder and Nason did not observe any significant differences in mean nickel concentration of hair samples between various age groups of men or women.

In the study by Nechay and Sunderman,[431] hair samples were restricted to segments of hair fibers no more than 5 cm from the scalp. The hair samples were washed with nonionic detergent and were digested with nitric and perchloric acids. Nickel in the digestion mixtures was chelated with ammonium pyrrolidone dithiocarbamate and extracted with methylisobutylketone before analysis by atomic-absorption spectrometry. The concentrations of nickel in 20 hair samples averaged 0.22 μg/g (range, 0.13–0.51; SD = ± 0.08). No significant difference was observed in mean nickel concentration of hair between men and women. There was a slight but significant diminution in hair nickel concentration with advancing age. According to Nechay and Sunderman, increased concentrations of nickel were observed in hair samples from subjects whose suboccipital hair exceeded 10 cm in length and subjects whose hair had been dyed or treated with "permanent wave" solution. The disparities between the results of Schroeder and Nason and those of Nechay and Sunderman are probably attributable to differences in sampling the hair and differences in techniques of washing the hair before analysis. Further investigations of nickel concentration in hair samples are needed before analysis of hair as a biopsy material can be accepted as an established method for estimating the body burden of nickel. Nonetheless, elimination of nickel in desquamated hair appears to be one of the physiologic routes for the excretion of nickel from the body.

The data concerning the concentrations of nickel in other biologic fluids and excreta are sparse. The presence of traces of nickel has been reported in synovial fluid by Niedermeier *et al.*,[436] in women's milk by Stovbun *et al.*[575] and Medvedeva,[396] and in sweat by Consolazio *et al.*[94] and Hohnadel *et al.*[251] Hohnadel *et al.*[251] measured nickel concentrations in sweat obtained from the arms of 33 healthy men and 15 healthy women during sauna bathing for 15 min at 93 C. The men sweated more profusely than the women: The volumes of sweat collected were 23 ± 12 ml (range, 3–55 ml) from the men and 7 ± 3 ml (range, 2–13 ml) from the women. The mean concentrations of nickel in the sweat samples were 52 ± 36 μg/liter (range, 7–182 μg/liter) in the men and 131 ± 65 μg/liter (range, 39–270 μg/liter) in the women. In contrast, the mean concentrations of nickel in serum and urine of healthy subjects, as measured in the same laboratory, were 2.6 ± 0.8 and 2.2 ± 1.2

μg/liter, respectively. Thus, sweating may provide an important route for the excretion of nickel from the body. Depletion of nickel may occur during prolonged exposure to heat. Conversely, sauna bathing may provide a therapeutic method for mobilization and elimination of nickel.[251]

Most nickel that is ingested orally is excreted in the feces. Horak and Sunderman[254] have measured fecal excretion of nickel during 3-day collection periods in 10 healthy subjects (six male and four female) who resided in Hartford, Connecticut. The mean nickel excretion in the feces averaged 3.3 ± 0.8 μg/g wet wt (range, 2.1–4.4 μg/g). When these data were expressed on the basis of dry weight of the feces, the fecal nickel averaged 14.2 ± 2.7 μg/g dry wt (range, 10.8–18.7 μg/g). Expressed as the average daily excretion of nickel during the 3-day collection periods, the mean fecal nickel was 258 ± 126 μg/day (range, 80–540 μg/day). Thus, the normal fecal excretion of nickel is approximately 100 times greater than the urinary excretion of nickel, which averaged 2.6 ± 1.4 μg/day in the same laboratory.

Partition in Serum of Man and Animals

Investigations in Sunderman's laboratory[234,447,448,609,670] have demonstrated that nickel is present in normal human and rabbit serum in three forms—as ultrafiltrable nickel, as albumin-bound nickel, and in a nickel metalloprotein that has been named "nickeloplasmin." Hendel and Sunderman[234] reported that the mean concentrations of total serum nickel in men, dogs, rabbits, rats, and lobsters were 0.23, 0.23, 0.90, 0.66, and 0.88 μg/100 ml, respectively. The ultrafiltrable fractions of nickel in these species averaged 41%, 85%, 16%, 27%, and 38%, respectively, of the total serum nickel. According to Callan and Sunderman,[71] the species variations in the partitions of serum ultrafiltrable and protein-bound nickel result, at least in part, from species differences in the nickel-binding properties of serum albumin. Callan and Sunderman[71] showed that the affinities of canine and porcine serum albumin for $^{63}Ni(II)$ are substantially less than the affinities of human, rabbit, and rat serum albumin. They reported that the first association constants of serum albumin for $^{63}Ni(II)$ were: dog albumin, 5×10^4 liters/mole; pig albumin, 1.6×10^5 liters/mole; rat albumin, 4×10^5 liters/mole; human albumin, 6×10^5 liters/mole; and rabbit albumin, greater than 6×10^5 liters/mole.

Von Soestbergen and Sunderman[670] injected radioactive nickel chloride ($^{63}NiCl_2$) intravenously into rabbits and found that an average of 90% of the serum nickel-63 became bound to albumin and 10% was ultrafiltrable during the 24 h after injection. Chromatography of serum ultrafiltrates on Sephadex G-25 demonstrated the presence of five distinct nickel-63 complexes. Three of the complexes were also found in the rabbits' urine. The chemical identities of the ultrafiltrable nickle-63 complexes in serum and urine have not been established, although one of them (fraction V) resembles nickel histidine in its chromatographic mobility on Sephadex G-25. The study by Von Soestbergen and Sunderman demonstrates that ultrafiltrable nickel in serum and urine does not exist primarily as free Ni(II), but occurs in the form of nickel complexes. Their study suggests that the ultrafiltrable nickel receptors play an important physiologic role in nickel metabolism by serving as diffusible vehicles for the extracellular transport and renal excretion of nickel. Asato *et al.*[16] have confirmed the presence of ultrafiltrable nickel-63 complexes in serum of rabbits after intravenous injection of $^{63}NiCl_2$, by use of thin-layer chromatography and autoradiography. Their study substantiates the role of ultrafiltrable complexes in the excretion of nickel.

Nomoto *et al.*[448] found that one fraction of protein-bound nickel in normal rabbit serum is present in an alpha-macroglobulin, which they named "nickeloplasmin." They showed that nickel-63 was present in the nickeloplasmin fraction of rabbit serum after daily intravenous injections of tracer doses of radioactive nickel chloride for 14–21 days. According to Nomoto *et al.*,[447,448] Sunderman *et al.*,[609] and Decsy and Sunderman,[117] serum nickeloplasmin has been isolated from human and rabbit serum and has been found to be a macroglobulin with an estimated molecular weight of 7×10^5 and an electrophoretic mobility in the alpha-globulin region. Nickeloplasmin gives a positive reaction to periodic acid Schiff stain for glycoproteins, and it possesses esterolytic activity, on the basis of its capacity to hydrolyze tritiated tosyl-arginine methylester at a pH of 7.5 in tris-HCl buffer. Nickeloplasmin is presumed to be identical with the nickel-containing metalloprotein that was first isolated from human serum by Himmelhoch *et al.*[248] Although nickeloplasmin resembles the zinc-containing macroglobulin that has been isolated from human serum by Parisi and Vallee,[461] it can be separated from the zinc-containing macroglobulin of column chromatography on DEAE–cellulose.[448,609]

There are not yet any available data on the physiologic significance of serum nickeloplasmin or on changes in the concentrations of serum nickeloplasmin that may occur in pathologic conditions. The alterations in concentration of total serum nickel that have been found in common human diseases and other conditions are discussed later in this chapter.

Distribution in Organs and Tissues

There are approximately 10 mg of nickel in a normal man, with wide individual variations.[528] Most of the available information pertaining to its distribution in organs and tissues of man is based on the work of Tipton and her colleagues.[473,643,645,647] Analysis was by emission spectrography. Two autopsy populations were chosen as subjects: apparently healthy Americans who had died suddenly and had no apparent disease at the time of death and foreign adults from the Eastern Hemisphere, many of whom had been chronically ill. The analytic results were treated separately, because different methods of preservation were used.

In the first group (subjects from the United States), tissues from 200 subjects from nine cities were analyzed. The methods of collection, sample preparation, and chemical and statistical analysis of tissues from 173 of these from eight cities, undertaken at the University of Tennessee, are described by Tipton *et al.*[645] Tissues from the other 27 subjects, from San Francisco, were analyzed at Oak Ridge National Laboratory by Koirtoyohann and Feldman.[312] Their methods were comparable, the only differences being in the limits of sensitivity for some elements. Nickel was observed in only about one-third of all samples analyzed, although it was observed in every tissue. The greatest frequency and the highest concentration occurred in skin.

In the second group, tissues from some 200 subjects from outside the United States were analyzed.[646] Fewer than half the subjects were victims of sudden accidental death, but the tissues from which the samples were taken showed no gross abnormalities. In the U.S. subjects, fewer than 50% of the nickel concentrations in liver, kidney, aorta, heart, and spleen (and fewer than 10% of the concentrations in brain) equaled or exceeded the minimal measurable concentration; in the lung, the limit of detectability was 0.09 micromole/g of tissue ash, and the 90th-percentile concentration was 0.48 micromole/g of tissue ash. In organs of the adults from the Eastern Hemisphere, fewer than 50% of the nickel concentrations in liver, heart, spleen, and brain equaled or exceeded the minimal measurable concentration; in the kidney, the limit of detectability was 0.09 micromole/g of tissue ash, and the 90th-percentile concentrations in kidney, lung, and aorta were 0.46, 0.68, and 0.85 micromole/g of tissue ash, respectively. In the U.S. subjects, the 80% range could not be calculated for nickel. Of the organs of the subjects from the Eastern Hemisphere, the 80% range could be calculated only in the lung (7.6 micromoles/g of tissue ash) and in the aorta (9.4 micromoles/g of tissue ash).

Schroeder *et al.*[528] examined the nickel concentrations in the kidney and liver of man from all the foregoing areas of the world and compared them. This was done by the microanalytic method of Sandell[515] for biomaterial, which depends on the formation of a color with dimethylglyoxime (see Table 3-5). Nickel appeared to be more prevalent in these two organs in persons from other parts of the world than it is in most Americans. This difference did not hold for the lung.

The raw spectrographic data on American human tissues were also examined by age and city of origin.[528] The relative infrequency of the detection of nickel in most tissues made statistical analysis unrewarding. Its frequencies of occurrence in 1,154 tissue samples were: bone, 5%; liver, 25%; larynx, 31%; kidney, 38%; heart, 42%; trachea, 49%; aorta, 49%; and lung, 65%. But it was found in 87% of intestine and skin samples.

Koch *et al.*,[310] writing in 1956, found nickel by spectrographic analysis in most of the tissue samples they studied, which were taken from the bodies of eight males who had died suddenly and accidentally at the age of 7–56 years. Its highest concentrations were in small intestine and bladder. Some further measurements of nickel were attempted in a group of Finnish subjects by Forssen, but in most cases the analytic method was insufficiently sensitive to detect nickel.[164] Sunderman *et al.*[615] reported measurements of nickel by atomic absorption on tissues obtained at autopsy from four previously healthy persons who died suddenly by murder or suicide. The results of these measurements are given in Table 3-6.

Accumulation and Body Burden

There are scant published data linking nickel intake from the air with nickel retention in lung tissue. Tissue from the lungs of four deceased workers who were accidentally exposed to nickel carbonyl in Ontario was examined in 1955 (G. J. Stopps and J. McEwan, personal communication). One died directly as a result of the accident (in 1949); another was poisoned but recovered, and he died in 1955. Each of the four men had 10–25 years of calcining or sintering experience in a very dusty atmosphere where the dust would have a high metal content. Lung tissue from six nickel miners was also examined in 1955; these men were exposed to dusts of low metal content. A group of "normal" lungs was examined in 1957 (G. J. Stopps and J. McEwan, personal communication). Comparison among these groups shows a clear gradient of nickel content, from very high in the men who suffered from the nickel carbonyl exposure to much lower in the miners to slightly lower still in the normal subjects (see Tables 3-7 through 3-9). Details of the prepa-

TABLE 3-5 Nickel Concentrations in Kidney and Liver, by Geographic Area[a]

Area	Kidney			Liver		
	No. Samples	Mean Nickel Concentration, ppm of ash[b]	Frequency of Nickel Occurrence, %	No. Samples	Mean Nickel Concentration, ppm of ash[b]	Frequency of Nickel Occurrence, %
United States	161	7	27	163	6	22
Alaska	2	35	100	1	36	100
Honolulu	5	4	40	5	4	40
Bern	9	11	100	9	7	67
Tokyo	10	7	80	10	10	70
Kyoto	11	10	55	9	8	67
Taiwan	9	16	78	9	10	89
Hong Kong	10	9	60	10	5	20
Manila	4	12	75	4	45	75
Bangkok	10	7	50	10	7	30
Bombay	9	28	89	9	20	56
Vellore	11	25	9	13	0	0
Delhi	10	22	100	10	14	90
Beirut	6	0	0	6	0	0
Cairo	3	5	33	2	0	0
Nigeria	19	8	58	17	30	6
Lambarene	5	<5	20	5	0	0
Welkom	5	23	80	3	0	0
Uganda	4	0	0	4	0	0
Usumbura	11	12	64	11	9	82
TOTALS (excluding U.S.)	146	12.4	58.2	141	11.0	44.0

[a] Derived from Schroeder *et al.*[536-538]

[b] Median percent ash of kidney was 1.1% (90% range, 0.8-1.3%), and of liver, 1.3% (90% range, 1.0-1.8%).

TABLE 3-6 Nickel Concentration in Human Tissues[a]

			Nickel Concentration, μg/100 g					
			Wet Weight			Dry Weight		
Subject	Age, years	Cause of Death	Lung	Liver	Heart	Lung	Liver	Heart
1 (male)	44	Stab wounds	2.40	0.52	0.62	14.6	2.1	2.3
2 (female)	40	Barbiturate poisoning	2.20	0.86	0.57	12.1	3.2	2.4
3 (male)	18	Hanging	0.81	0.76	0.43	3.3	2.6	1.6
4 (female)	22	Carbon monoxide poisoning	0.96	1.32	0.83	4.3	4.8	3.0
MEAN			1.59	0.87	0.61	8.6	3.2	2.3

[a] Derived from Sunderman *et al.*

TABLE 3-7 Nickel in Lungs of Victims of Nickel Carbonyl Poisoning in Ontario[a]

		Nickel Concentration, μg/100 g		
Tissue	Subject[b]	Wet Weight	Dry Weight	Ash
Right lung (part not known)	A	6.6	32	900
Right lung, upper lobe	B	11.9	79	1,800
	C	13.9	90	1,950
	D	21.1	128	2,600
Left lung (part not known)	A	7.8	46	1,050
Left lung, lower lobe	B	7.4	47	1,100
	C	7.8	44	1,150
	D	11.1	65	1,300

[a] Data from G. J. Stopps and J. McEwan (personal communication).

[b] Subjects A, B, and C died in 1949; subject D, in 1955.

TABLE 3-8 Nickel in Lungs of Ore Miners in Ontario

		Nickel Concentration, μg/100 g	
Miner	Duration of Exposure, yr	Dry Weight	Ash
1	27	0.86	8
2	19	0.25	6
3	20	0.22	7
4	21	0.49	12
5	17	1.36	13
6	39	0.48	10

TABLE 3-9 Nickel in Normal Lungs of Ontario Subjects

				Nickel Concentration, μg/100 g		
Subject	Sex	Age, yr	Cause of Death	Wet Weight	Dry Weight	Ash
E	Male	50	Rupture of intracerebral aneurysm	0.018	0.091	4.0
F	Male	52	Berry aneurysm, left internal carotid	0.021	0.119	2.0
G	Male	71	Carcinoma of prostate	0.021	0.175	5.0
H	Male	75	Myocardial infarction	0.017	0.116	4.8
I	Female	23	Subarachnoid hemorrhage	0.009	0.060	4.0
J	Female	35	Carcinoma of cervix; pelvic abscess	0.010	0.102	5.0
K	Female	48	Uremia; recent myocardial infarction	0.014	0.083	5.0

ration of the tissue and of the analysis (a colorimetric estimation using dimethylglyoxime) are not known. (Measurements of the distribution of nickel-63 in organs and tissues of rodents after injections of $^{63}NiCl_2$ are discussed in Chapter 4.)

BINDING TO BIOLOGIC SUBSTANCES

A complete understanding of the biologic effects of nickel depends on knowledge of the nickel binding sites within the human cell and knowledge of the effect on cellular behavior of nickel binding to a particular site. Because relatively little is known about the molecular sites attacked by nickel within the cell, it is of some interest to consider reactions of nickel ions with molecules that have been isolated from the cell. A comprehensive survey of nickel binding to biologic substances is beyond the scope of this work, but a cursory examination of nickel binding and its possible implications will be provided.

Nickel binding to biologically important substances has usually been studied in the context of the binding of metal ions in general. The effects of nickel are only occasionally unique; generally, they are illustrative of the effects of metal ions, particularly ions of the first transition series, to which nickel belongs. Nickel in its common oxidation state of 2+ is nevertheless somewhat unusual in its potentialities, in that it is capable of existing in and being readily interconverted among three different geometric structures—square planar, octahedral, and tetrahedral.

Binding to Nucleic Acids

Nickel ions and other metal ions exert profound effects on genetic material. It was discovered by Wacker *et al.*[184,684,685] that RNA is isolated in association with metal ions, including Ni(II), that are tightly bound to the nucleic acid molecule. The nickel contents of RNA from various sources, as determined by spectrographic analysis, are listed in Table 3-10 It has been demonstrated (Eichhorn and Shin[141] and Shin *et al.*[544]) that Ni(II) binds to both the phosphates and the heterocyclic bases of DNA and RNA and stabilizes the conformation of RNA[184] and DNA. When RNA is heated with nickel, phosphodiester bonds are broken, and the macromolecule is depolymerized.[69,262,382] These effects indicate that nickel can have a rather dramatic impact on genetic material. The binding of nickel to DNA could be significant in the inhibition of RNA polymerase, as discussed in Chapter 6.

Binding to Nucleic Acid Monomers and Related Compounds

The biologic synthesis and degradation of nucleic acids involve the monomeric constituents of the nucleic acids (the nucleotides), which bind to nickel primarily through the phosphate groups, but also by base binding.[523,564,565] This binding is perhaps particularly significant when it occurs with adenosine triphosphate (ATP), an extremely important cellular constituent involved in energy transfer and a multitude of enzymatic reactions.[61,62,200,523,534,546,701]

Ni(II) has also been shown to bind to both the pyrophosphate group and the pyrimidine base of thiamine pyrophosphate, a substance that acts as a coenzyme in many enzymatic reactions.[712]

TABLE 3-10 Nickel Content of RNA From Various Sources[a]

RNA Source	Nickel Concentration, μg/g of RNA
Calf pancreas	130
Calf thymus	74
Horse kidney	44
Rabbit reticulocyte	51
Euglena gracilis	60
Rat liver	64

[a] Derived from Wacker and Vallee.[685]

Binding to Proteins

If binding of nickel ions to nucleic acids and their constituents can influence the transfer of hereditary information, binding to proteins can change the conformation of these substances, which are primarily responsible for the structure of the cell and the course of enzymatic processes. The binding of metal ions generally and nickel specifically has been most widely studied with bovine and human serum albumin because of the ready availability of these proteins.[89,100,352,489,490] Carboxyl groups[490] and imidazole groups[489] have been implicated as the binding sites, as have the alpha-amino group of aspartic acid,[476] the terminal amino group and the adjacent peptide, and a sulfhydryl group.[654] The interaction of Ni(II) with terminal amino groups and adjacent peptide nitrogen atoms has also been postulated with lysine, vasopressin, conalbumin, alpha-chymotrypsin, ribonuclease,[654] and myoglobin.[65] Ni(II) binding to casein, gelatin, pseudoglobulin, and keratin has also been noted.[100]

Binding to Peptides

Oligopeptides are products of protein disintegration and thus occur in biologic systems. The study of Ni(II) binding to these substances is of added interest, in that it serves as a simplified model of Ni(II)–protein interaction. The Ni(II) complexes of diglycine and triglycine have been studied by x-ray crystallography.[167] In the diglycine complex, the nickel is bound to all three possible electron donor sites: carboxyl, peptide nitrogen, and amino group. In the triglycine complex, in which chelation could involve either the peptide and the carboxyl group or the peptide and the amino group, the latter combination actually participates in the chelation, confirming the tendency of proteins to bind at these sites. Complex formation of peptides with Ni(II) has also been studied in solution, and it has been established that nickel coordination can displace a proton from the peptide linkage.[64,137,303,336] Most evidence indicates that the nickel binds to the nitrogen of the peptide link in solution, as in the solid state, although binding to carbonyl oxygen has also been suspected.[23] The ability of nickel to form paramagnetic octahedral complexes, as well as diamagnetic square planar complexes, has been demonstrated with triglycine[376] and more complex peptides.[64] The blue octahedral complexes are converted into yellow square planar complexes by titrations in which the coordination sites around the nickel are rearranged. Solution studies confirm the ability of nickel to bind to terminal amino groups and peptide and carboxyl linkages.[64, 303]

When amino acids containing sulfur or heterocyclic nitrogen atoms are incorporated in a peptide, these electron donor atoms also participate in the coordination with nickel. The imidazole nitrogen is implicated in the binding of nickel to glycyl-L-histidine and L-histidyl-L-histidine,[64,377] and cysteine sulfur is involved in the binding to glutathione.[82] The conversion of an octahedral nickel complex to a square planar complex can also be promoted by titration with base in the case of glycyl-L-histidine; the transition is accompanied by scission of the bond between nickel and the amino group.[377] The ready convertibility of nickel from the octahedral to the square planar configuration is emphasized because of the possibility that the toxicity of the metal in these various forms could differ significantly, although no information about this matter is available.

The octapeptide Val^5-angiotensin II-Asp^1-β-amide has been shown to form a nickel complex.[547] Complex formation results in the catalysis of the cleavage of the peptide by peroxide. The binding sites of nickel on the peptide are not known.

Binding to Amino Acids

Amino acids are not nearly as good models as peptides in the probe of metal interaction with proteins, because isolated amino acids lack peptide bonds, which generally are involved in the chelation of nickel to both peptides and proteins. The presence of strongly coordinating functional groups on amino acids—such as the heterocyclic nitrogen atoms of histidine and the sulfur atoms of cysteine—and the existence of individual amino acids as cellular constituents provide some interest for considering the nickel complexes of amino acids that are not involved in peptide linkages.

Nickel has a high affinity for sulfur; cysteine has three potential donor atoms—carboxyl, sulfhydryl, and amino—of which only the latter two are coordinated, leaving the carboxyl group unbound.[82,152,711] Other sulfhydryl amino acids—e.g., methionine, ethionine, and penicillamine—bind nickel in the same fashion as cysteine.[336] When cysteine is dimerized into cystine, the two sulfur atoms are bonded to each other in a disulfide linkage, which has been postulated to be inactive in the formation of a nickel complex.[491]

Histidine binds nickel through the heterocyclic nitrogen. The related histamine likewise binds to the ring nitrogen, forming a chelate by simultaneous coordination of the amino group.[226]

Amino acids that do not contain unique functional groups chelate through the carboxyl and alpha-amino groups characteristic of all amino acids. Proline is the only amino acid that contains no alpha-amino group; however, the presence of one or two hydrogen atoms on the nitrogen atom appears to make no difference in the coordination properties of the amino acid, and nitrogen–oxygen chelation occurs also in the nickel–proline complex.[238]

Binding to Vitamin B_6 and Transamination

Ni(II) reacts with all active forms of vitamin B_6, such as pyridoxal and pyridoxamine.[140,340] Like other metal ions, nickel ions can catalyze transamination—i.e., the transfer of an amino group from an amino acid to a keto acid—in the presence of the vitamin.[346,401-403] The catalysis proceeds through the formation of a nickel complex of the Schiff base between the keto acid and pyridoxamine, followed by a tautomeric shift of a double bond that converts the initially produced Schiff base into the Schiff base of pyridoxal and the amino acid corresponding to the keto acid. Hydrolysis then yields that amino acid in its free form. The reversal of these steps, beginning with pyridoxal and an amino acid, similarly produces pyridoxamine and a keto acid. The combination of these two reversible processes, with both an amino acid and a keto acid present, brings about the donation of the amino group from the amino acid to the keto acid.[140,401-403]

Nickel Complexes of Porphyrins and Related Compounds

Porphyrins—which are essential constituents of many enzymes, hemoglobin, and, in modified form, chlorophyll—form complexes with many metal ions, including nickel ions.[149] Nickel–porphyrin complexes are indeed found in petroleum,[137] although the origin of these substances is not understood Inasmuch as uroporphyrins, like porphyrins generally,[149] readily form nickel complexes under physiologic conditions, it has been postulated that nickel could interfere with such biologic processes as hemoglobin and chlorophyll biosynthesis.[175] Nickel ions, like other metal ions, form a complex with bilirubin (a porphyrin derivative with one meso bond broken), but the bilirubin in complexed form readily decomposes.[672]

Other Divalent Nickel Complexes

It has been shown that Ni(II) binds to the phospholipids triphosphoinositide and phosphatidylserine[235] and that the nickel already bound to these substances can bind additionally to polypeptides and proteins. This suggests a mechanism by which nickel could be involved in lipoprotein formation.[176]

Ni(II) chelates with dihydrolipoic acid, presumably through the two sulfhydryl groups, and this chelation could interfere with such processes as the utilization of pyruvic acid in the formation of acetyl coenzyme A.[691] Ni(II) binds to acetyl coenzyme A,[563] to citric acid,[242] and to phytic acid.[674]

Stability Constants

The relative stabilities of metal complexes provide a measure of the relative affinities of the metals for the ligands to which they are bound. The stability constants of some of the nickel complexes discussed above and in the section on enzymatic activities immediately following are listed in Table 3-11 as a guide to the most likely associations that nickel can be expected to make in a biologic medium. It should be pointed out that such a comparison of stability constants can be misleading. One reason is that complexes that are thermodynamically stable may have little chance of being produced because of kinetic barriers. Another is that a stable nickel complex may have much less physiologic significance than a less stable complex.

TABLE 3-11 Some Stability Constants of 1:1 Ni(II) Complexes with Biologic Substances

Ligand	Stability (log K)	Authors
Adenosine	0.17	Schneider *et al.*[513]
Adenosine triphosphate	4.54	Brintzinger[62]
Diglycine	3.34	Kim and Martell[303]
Triglycine	3.76	Kim and Martell[303]
Tetraglycine	3.65	Kim and Martell[303]
Carnosine	5.42	Lenz and Martell[336]
Histidine	8.7	Li *et al.*[342] Leberman and Rabin[330] Chakravorty and Cotton[80]
Methionine	5.14	Lenz and Martell[336]
Ethionine	6.15	Lenz and Martell[336]
L-cysteine	9.64	Lenz and Martell[336]
Penicillamine	11.11	Lenz and Martell[336]
Citrate	4.40	Heitner-Wirguin *et al.*[242]
Phosphoglyceric acid	2.88	Wold and Ballou[719]
Phosphoenolpyruvic acid	2.34	Wold and Ballou[719]
Bovine serum albumin	3.17	Rao[489]
Carboxypeptidase	8.2	Coleman and Vallee[92]
Carbonic anhydrase	9.5	Lindskog and Nyman[343]

Conclusions

It is clear from this cursory discussion of nickel binding to biologic substances that nickel can bind to a large variety of molecules that are found in the cell. Much of the information available from the literature reflects the interests of scientists who have been motivated by objectives other than the desire to elucidate the environmental effects of nickel. This survey can therefore only indicate some of the many ways in which nickel can interfere with or participate in cellular processes, but it cannot at this time pinpoint mechanisms for the physiologic effects of this metal.

EFFECTS ON ENZYMATIC ACTIVITIES

Metal ions are integral parts of many enzyme molecules. When the metal ion is removed from the protein component of such an enzyme, enzymatic activity is lost. Many other enzymes that are isolated from cells and have no metal attached to them nevertheless require the addition of metal ions to become active.[136,212,335,360,361,406,663–665,715] It is possible that the only difference between these two classes of enzymes is that the metal is attached more firmly to the former than to the latter, so that isolation leaves the metal–protein bonds intact in some instances and destroys them in other instances.

Activation versus Inhibition

Metal ions have been demonstrated to be part of the active site of a number of enzymes and are therefore of critical importance in the function of these enzymes. No enzyme has yet been found that contains nickel as an intrinsic ingredient. However, many metal ions are powerful inhibitors of enzymatic action. It is difficult to use the available literature to compare the activating and inhibiting capabilities of metals, including nickel, on the action of various enzymes, because different enzymes have been studied under different conditions.[138] The effects of a metal ion on an enzyme can vary greatly with experimental conditions. For example, the optimal concentration of Ni(II) for the activation of oxaloacetic decarboxylase[557] is 10^{-2} *M*; the activity of the enzyme decreases both below and above this Ni(II) concentration.

Enzymatic Cleavage of Nucleic Acids

The effect of variation in conditions on enzymatic activity is clearly seen in a comparison of the effects on ribonuclease activity of nickel at various concentrations.[139] Bovine pancreatic ribonuclease does not require the presence of divalent metal ions for its activity, but the activity can be more than doubled by the judicious selection of activating metal ions. As in the activation of decarboxylase, there is an optimal nickel concentration for ribonuclease activity $\sim 10^{-3}$ *M*. As the nickel concentration is increased beyond this optimum, ribonuclease activity decreases and eventually becomes greatly inhibited. Thus, nickel can both activate and inhibit ribonuclease, depending on its concentration. This phenomenon illustrates the caution that is required when interpreting published statements that a given enzyme is activated or inhibited by nickel. Such factors as concentration, pH, and ionic strength can make the difference between activation and inhibition.

Pancreatic deoxyribonuclease I requires divalent metal ions to be active, and nickel is an effective activator, although not as effective as several other metal ions.[139]

Carboxypeptidase and Carbonic Anhydrase

Although some enzymes are associated with a specific metal ion in the native state, the intrinsic metal can sometimes be removed and replaced by another metal. As Vallee and co-workers[92, 666] have demonstrated, nickel (and other metal ions) can replace zinc in carboxypeptidase. The activity lost when zinc is removed is restored when nickel is added to the apoenzyme.

Zinc is also the intrinsic metallic constituent of carbonic anhydrase (from bovine red cells). As in carboxypeptidase, the zinc can be replaced by nickel, and the nickel then occupies the same site to which the zinc had been attached. With carbonic anhydrase, unlike carboxypeptidase, the nickel enzyme has no activity.[91, 137]

Other Enzymes "Activated" by Nickel

Perhaps the first reported instance of metal activation of an enzymatic reaction was that of Hellerman and Perkins[233] regarding arginase; one of the effective metals is nickel (see also Greenberg *et al.*[207]). A number of studies have been carried out on the effect of metal ions, including Ni(II), on enolase, which requires divalent metal ions for its activity.[357-360,362,719,720] Ni(II) is a very effective activator for phosphoglucomutase.[468,469,492] Activation by nickel has been reported for the amino acid decarboxylases of *Escherichia coli* and *Clostridium welchii*,[135] acetyl coenzyme A synthetase,[696] pyridoxal phosphokinase,[266] thiaminokinase,[367] pyruvic acid oxidase,[579] human salivary amylase,[660] and citritase.[111] Ni(II) has also been shown to enhance the uptake of glucose into rat adipose tissue and the incorporation of glucose into glycogen.[121] These effects on glucose utilization may or may not result from enzyme activation.

Ribulose Diphosphate Carboxylase

Ribulose diphosphate carboxylase, which catalyzes the conversion of ribulose diphosphate into phosphoglyceric acid, deserves special mention here, because nickel ions are unique among the transition metal ions in stimulating this enzyme to maximal efficiency. Magnesium is equally effective, but transition metals other than nickel produce little or no activation.[702]

Enzymes "Inhibited" by Nickel Ions

Nickel ions have been observed to inhibit dialkylfluorophosphatase and aspartase.[145,422] The inhibition of RNA polymerase is discussed in Chapter 6. The effect of nickel on alkaline phosphatase appears to be controversial; although activation has been reported by Freiman,[170,171] Schwartz and Bodansky[535] have found inhibition. This discrepancy may be due to work with enzymes from different sources; the caution indicated above regarding activation and inhibition of enzymes under different conditions must be kept in mind. It has been demonstrated that nickel will bind to the same site of alkaline phosphatase as the native zinc.[328]

Of all the known inhibiting effects of Ni(II), the inhibition of phosphate cleavage in nucleotides, and particularly ATP, could be particularly significant. Nickel strongly inhibits 5′-nucleotidase—e.g., from bull seminal plasma[535]—and ATPase.[294,488] As has been noted, ATP is extremely important in many energy-producing and enzymatic biologic processes. Joó and co-workers[283,284,671] have given rats intravenous injections of nickel (II) chloride and have noted a loss of ATPase activity in the brain capillaries accompanied by a thickening of the basement membrane of the capillaries and the formation of collagen-like fibers. They propose that ATPase activity plays an important role in the regulation of the blood–brain barrier and that nickel, by inhibiting ATPase, therefore upsets this regulatory mechanism. Sunderman[597] has shown that nickel carbonyl also inhibits ATPase in rat liver and produces increased concentrations of ATP. It has been suggested that the Ni(II) inhibition of ATPase can be reversed by amino acids, possibly because the latter sequester the nickel and prevent it from exerting any effect on the enzyme.[150]

Conclusions

Ni(II) under various conditions can activate or inhibit numerous enzymatic reactions. Some of these reactions are crucial in the metabolism of humans and other animals, and interference with them could have severe deleterious effects.

ALTERATIONS OF NICKEL METABOLISM IN MAN IN VARIOUS COMMON DISEASES AND PHYSIOLOGIC STATES

Heart Diseases

D'Alonzo and associates[112,113] used emission spectrography to estimate trace-metal content of serum collected from 20 patients with acute myocardial infarction within 24 h after admission to the hospital. They observed that the serum nickel concentration was significantly increased in 19 of their 20 patients, and they speculated that nickel might be involved in the etiology of myocardial infarction or that an enzyme containing nickel might be released into the serum after myocardial infarction. Their data suggested that increased serum nickel concentrations were not found in other types of ischemic heart disease. Sunderman *et al.*[393,449,609,615,616] used atomic-absorption spectrometry to measure nickel content of serum from 42 patients with acute myocardial infarction. These workers found that serum nickel concentrations were normal or slightly increased during the first 12 h after onset of symptoms. However, during the next 12 h after the onset of symptoms, the mean serum nickel concentration was 0.52 ± 0.08 μg/dl, compared with 0.26 ± 0.08 μg/dl in serum from 47 healthy control subjects. Increased serum nickel concentrations were found in about 75% of the patients with myocardial infarction during the period from 13 to 36 h after onset.[396] Serum nickel concentrations were also increased in 25% of patients who were diagnosed as having acute myocardial ischemia without infarction. Therefore, measurements of serum nickel did not reliably discriminate between these two categories of disease.[393] Sunderman *et al.*[615] and Schroeder and Nason[531] have calculated that release of the nickel normally present in the heart would be insufficient to account for the observed hypernickelemia after acute myocardial infarction. Hence, it has been proposed[531,615] that cardiac tissue from patients with myocardial infarction may contain abnormally increased concentrations of nickel, or that the hypernickelemia after myocardial infarction may be caused by release of nickel from an extracardiac source, such as the lungs or liver.

The only studies in experimental animals that are directly related to nickel metabolism in myocardial infarction have been reported by Ryabova,[503-505] who measured nickel concentrations in serum and myocardium from 36 dogs after provoking acute myocardial ischemia by ligating the left coronary artery for 10–60 min. According to Ryabova, the mean myocardial nickel concentration was significantly increased after myocardial ischemia, but there was no significant alteration in the mean serum nickel concentration.

Pauk[465] has measured nickel concentrations in blood specimens from children with acute rheumatic fever and has observed increases in blood nickel in some of the children with cardiac involvement. It is difficult to assess the validity of the analytic method used in Pauk's investigation.

Liver Diseases

McNeely *et al.*[393] have reported significant diminutions in the mean nickel concentration in serum from patients with hepatic cirrhosis. Approximately one-fourth of their patients with hepatic cirrhosis had serum nickel concentrations below the normal range. The hyponickelemia in hepatic cirrhosis is attributable to a diminished concentration of serum albumin, which is the major nickel-binding protein. Volini *et al.*[678, 679] have found that hepatic nickel concentrations were significantly increased in both the early and the advanced stages of hepatic cirrhosis. Sukharev and Chistyakov[580] have observed increased serum nickel concentrations in some patients with viral hepatitis and have noted a correlation between serum bilirubin and nickel concentrations.

Burns

Using spectrographic analysis, Silvestri[548] detected nickel in serum from patients with extensive burns and did not detect any nickel in serum from healthy control subjects. Using atomic-absorption spectrometry, McNeely *et al.*[393] confirmed the marked increase in serum nickel in severely burned patients during the period from 37 to 72 h after injury.

Acute Stroke

McNeely *et al.*[393] observed increased serum nickel concentrations in 6 of 12 patients with acute cerebral stroke during the period from 37 to 72 h after the onset of symptoms.

Septicemia

Sunderman (personal communication) observed increased serum nickel concentrations in two of three patients with septicemia due to gram-negative bacteria. The serum specimens were obtained between 13 and 37 h after the onset of septicemia.

Kidney Diseases

Mertz *et al.*[394] have found that urinary excretion of nickel in patients with renal insufficiency is positively correlated with urine volume and is largely independent of the degree of impairment of renal function, as measured by insulin and *p*-aminohippurate clearances. McNeely *et al.*[393] measured serum nickel concentrations in patients who had chronic uremia resulting from glomerulonephritis, pyelonephritis, diabetic nephrosclerosis, or malignant essential hypertension. The mean serum nickel concentration was significantly diminished in the uremic patients, and serum nickel concentration was positively correlated with serum albumin concentration.

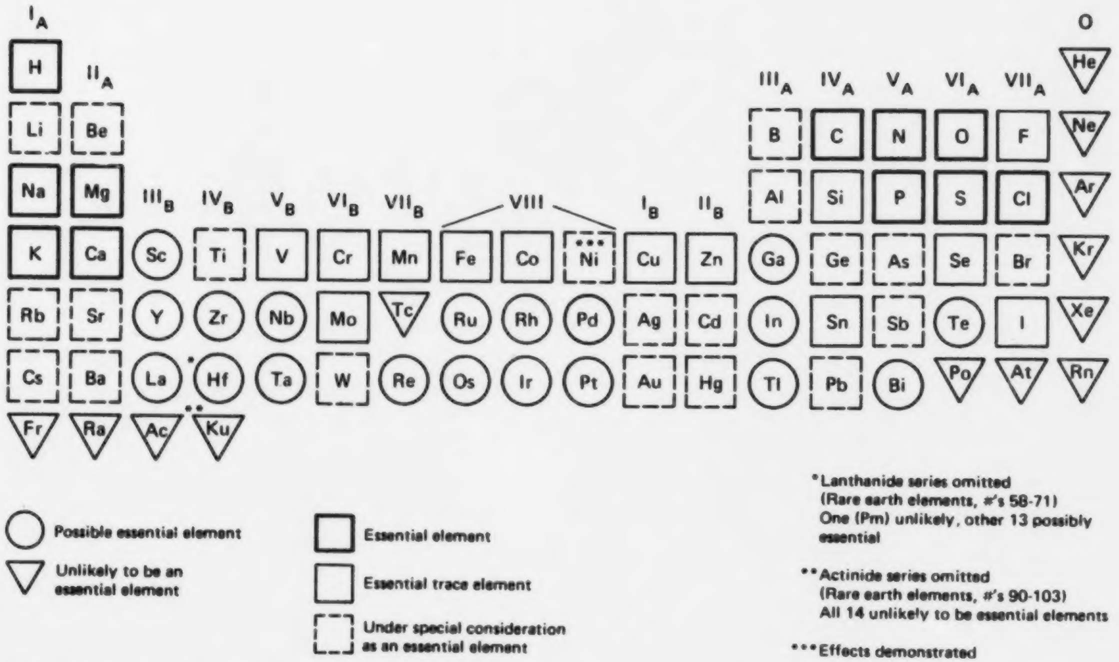
Heat Stress

Szadkowski *et al.*[627] found marked diminutions in serum nickel concentration in steel-mill workers who were exposed to extreme heat stress. This observation is especially noteworthy, in view of the reports by Consolazio *et al.*[94] and Hohnadel *et al.*[251] that volunteers who were exposed to environmental heat lost appreciable quantities of nickel in their sweat.

Miscellaneous Conditions

McNeely *et al.*[393] have failed to detect any significant alterations of serum nickel concentration in patients with acute trauma and fractures of bones, patients with muscular dystrophy, newborn infants, or post-partum women. Niedermeier *et al.*[436,437] have estimated nickel concentrations in serum and synovial fluid from patients with rheumatoid arthritis and have failed to detect any abnormalities. It should be noted that their spectrographic method was relatively insensitive and that they failed to detect any nickel in serum from 43% of their control subjects.[398]

Herring *et al.*[239] also used emission spectrography to estimate nickel concentrations in plasma and red blood cells from patients with a variety of hematologic diseases. They found the nickel concentrations to be


I A
II A
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VII B
VIII
I B
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III A
IV A
V A
VI A
VII A
O
H He
Li Be B C N O F Ne
Na Mg Al Si P S Cl Ar
K Ca Sc Ti V Cr Mn Fe Co Ni Cu Zn Ga Ge As Se Br Kr
Rb Sr Y Zr Nb Mo Tc Ru Rh Pd Ag Cd In Sn Sb Te I Xe
Cs Ba La Hf Ta W Re Os Ir Pt Au Hg Tl Pb Bi Po At Rn
Fr Ra Ac Ku
Possible essential element
Unlikely to be an essential element
Essential element
Essential trace element
Under special consideration as an essential element
*Lanthanide series omitted (Rare earth elements, #'s 58-71) One (Pm) unlikely, other 13 possibly essential
**Actinide series omitted (Rare earth elements, #'s 90-103) All 14 unlikely to be essential elements
***Effects demonstrated

FIGURE 3-1 Periodic chart of the elements, showing known and potential importance for mammalian organisms. Derived from Schwarz.[536]

highly variable, and they stated that no valid conclusions could be drawn from their data.

Various publications have cited measurements of nickel concentration in serum from patients with leukemia,[338,426] uterine cancer,[15,506] skin diseases,[154,339] rheumatic diseases,[116] pneumonia,[622] toxemia of pregnancy,[337] and schizophrenia[556] and from animals with irradiation diseases.[56,437] Unfortunately, valid interpretation of these data is precluded by limitations in the sensitivity and precision of the methods used for nickel measurements.

EVIDENCE THAT NICKEL IS AN ESSENTIAL ELEMENT

The periodic chart of the elements shown in Figure 3-1 indicates the 23 elements currently considered as essential to the life or health of animals.[400,536,537,541] The location of nickel (atomic number 28) in the midst of the row of essential trace metals that extends from vanadium to zinc has suggested to some authors[400,527,531,536,541] that nickel is also likely to be an essential element. Shaw[541] and Mertz[400] have noted that nickel is especially suited for a biochemical role, in that it readily undergoes transitions among several coordination structures. Indeed, recent evidence suggests that nickel partially satisfies the criteria[400] for essentiality of trace elements as micronutrients: presence of the element in the fetus or newborn, presence of homeostatic regulation of the metabolism of the element, demonstration of a metabolic pool of the element that is specifically influenced by hormonal substances or pathologic processes, demonstration of a metalloenzyme of which the element is an integral part, and demonstration of a deficiency syndrome that can be prevented or cured by trace amounts of the element.

Presence of Nickel in the Fetus and Newborn

Schroeder and associates[528] have shown that nickel occurs in human fetal tissues and have therefore concluded that nickel can cross the human placenta. This conclusion has been corroborated by McNeely and co-workers,[393] who found that the mean concentration of nickel in cord serum from 12 neonates (0.30 ± 0.12 μg/dl; range, 0.17–0.49 μg/dl) was identical with that in serum from their mothers immediately after delivery (0.30 ± 0.12 μg/dl; range, 0.13–0.49 μg/dl). Mertz[400] has cautioned that "the presence of an element in a growing fetus or in the newborn is compatible with, but not indicative of essentiality, since even the transfer of a substance from mother to fetus may be nonspecific and reflect contamination of the maternal organism."

Homeostatic Regulation of Nickel Metabolism

Evidence of homeostatic regulation of nickel metabolism includes the report by Nomoto *et al.*[448] that serum nickel is normally maintained within relatively narrow and characteristic concentration ranges in 16 different animal species, the demonstration by Mertz and co-workers[398] that the human kidney possesses an active excretory mechanism for nickel, and the finding by Nielsen and Sauberlich[442] that chicks fed a diet containing nickel at less than 80 ppb incorporated greater proportions of a tracer dose of nickel-63 in liver, spleen, and aorta than did control chicks fed the same diet with supplemental nickel.

Effects of Hormonal Substances and Pathologic Processes on Metabolic Pools of Nickel

There is no evidence that metabolic pools of nickel are specifically altered by endocrine factors or hormonal substances. There are no significant differences in serum nickel concentrations between males and females of any species studied,[447] no significant alterations in serum nickel concentration occur at the end of normal human gestation,[393] and administration of estradiol-17β (50 μg/day subcutaneously for 42 days) to ovariectomized rats did not produce any significant alterations in mean serum nickel concentration (unpublished observation of Sunderman and Nomoto). Alterations of metabolic pools of nickel do occur in several common human diseases. The pertinent evidence includes the observations by D'Alonzo and Pell[112] and Sunderman *et al.*[616] that mean serum nickel concentrations are significantly increased after myocardial infarction, the findings by McNeely and associates[393] that mean serum nickel concentrations are increased after stroke and burns and decreased in hepatic cirrhosis and chronic uremia, and the report by Volini *et al.*[678] that hepatic nickel concentrations are increased in hepatic cirrhosis.

Identification of a Serum Nickel-Containing Metalloprotein

Himmelhoch and co-workers[248] have reported the occurrence in human serum of a metalloprotein that is rich in nickel and does not contain other detectable trace metals. Nomoto *et al.*[447, 448] and Sunderman and co-workers[609] have confirmed the existence of a nickel-containing metalloprotein (nickeloplasmin) in human and rabbit serum. According to Sunderman *et al.*,[609] nickeloplasmin is an alpha-macroglobulin and possesses the trypsin–protein esterase activity that is a general property of serum alpha-macroglobulins.

Nickel Deficiency in Experimental Animals

Attempts to produce nickel deprivation in experimental animals are summarized in Table 3-12. The investigations of Smith[553] and of Wellenreiter and associates[704] failed to produce any consistent effects of nickel deprivation. Nielsen and co-workers[439,440,442] reported a nickel-deficiency syndrome in chicks fed diets containing nickel at 40–80 ppb. In comparison with control chicks, fed identical diets with added nickel (3–5 ppm as nickelous chloride hexahydrate), Nielsen and associates observed that nickel-deprived chicks had swollen hock joints, reduced length : width ratios of the tibias, yellow–orange discoloration, scaly dermatitis of the legs, and fat-depleted livers. Sunderman *et al.*[614] fed chicks a similar diet, which contained nickel at 44 ppb. In their study, the nickel-deprived chicks did not develop the nickel-deficiency syndrome described by Nielsen and co-workers, but they did have significant diminutions in mean serum and hepatic nickel concentrations. Moreover, Sunderman *et al.*[614] observed perimitochondrial dilatation of rough endoplasmic reticulum in the hepatocytes of nickel-deprived chicks. According to Piccardo and Schwartz,[482] such perimitochondrial dilatation of endoplasmic reticulum may be the earliest ultrastructural lesion in dietary degeneration of hepatocytes. Nielsen and Ollerich[441] fed chicks a diet containing nickel at 3–14 ppb, and they confirmed the occurrence of ultrastructural abnormalities in hepatocytes, similar to those observed by Sunderman *et al.*[614] Nielsen and Ollerich[441] were unable to reproduce their earlier findings of abnormalities in leg structure in nickel-deprived chicks. They mentioned preliminary observations that rats fed a diet containing nickel at 3–14 ppb developed abnormalities of hepatic metabolism similar to those seen in nickel-deficient chicks. On the basis of reports of Nielsen *et al.*[440-442] and Sunderman *et al.*,[614] the dietary essentiality of nickel appears to be highly probable, but not yet conclusively demonstrated.

Conclusions

From the evidence presented, it appears that nickel partially satisfies Mertz's criteria for the essentiality of a micronutrient.[400] Therefore, it may be concluded that nickel is probably essential for animal nutrition.

TABLE 3-12 Studies of Nickel Deprivation in Experimental Animals

Authors	Species	Nickel Concentration in Diet, ppb	Duration of Experiment	Observations
Smith[553]	White rats	80	55 days	No effects
Wellenreiter *et al.*[703]	Coturnix quail	74	4 generations	No effects
Nielsen *et al.*[439, 440, 442]	White rock and New Hampshire red chicks	40–80	4 weeks	Increased nickel-63 uptake in liver, spleen, and aorta; discoloration, dermatitis, and deformity of legs; fat-depleted livers
Sunderman *et al.*[614]	White rock chicks	44	30 days	Decreased serum and hepatic nickel content; dilatation of perimitochondrial endoplasmic reticulum of hepatocytes
Nielsen and Ollerich[441]	Golden giant chicks	3–14	25 days	Dilatation of cisternae of endoplasmic reticulum in hepatocytes; swelling of hepatocyte mitochondria

However, there has not yet been unequivocal demonstration that nickel deprivation produces consistent abnormalities in experimental animals that can be prevented or cured by the administration of nickel.

NICKEL AND EXCITABLE TISSUES

The major effects of nickel on excitable tissues (nerve; skeletal, cardiac, and smooth muscle; nerve–muscle junction; and central nervous system) can be described as competitive with and imitative of those of calcium. Nickel binds more strongly than calcium to the reactive groups of protiens ($-NH_2$, $-COO^-$, OH, SH),[212] as well as to membranes.[216] Once nickel has bound to the membrane or active site, its ability to mimic calcium varies widely from tissue to tissue. In general terms, nickel causes a prolonged action potential and an uncoupling between membrane activity and muscle contraction. This nickel-induced uncoupling does not occur in the presence of millimolar concentrations of calcium. The increased duration of the action potential occurs in the presence of calcium and has a threshold of 10^{-5} *M* nickel.

Excitable Membranes

The major effect of Ni^{2+}, either in replacement of or in addition to Ca^{2+}, is to increase the duration of the action potential. The nodes of Ranvier respond to the substitution of Ni^{2+} for Ca^{2+} by a 15-fold increase in action-potential duration.[559] The rates of rise and fall are markedly diminished, so the Ni^{2+} action potential resembles the cardiac ventricular action potential. The overshoot is unaffected.[300, 302, 630] The threshold for this effect is 5×10^{-6} *M* nickel chloride, either in addition to or substituted for the normal calcium chloride. The mechanism of action is thought to be as follows: "the prolongation of the nodal action potential by $NiCl_2$ is due to delayed and reduced inactivation of sodium permeability and delayed increase of potassium permeability."[404]

These effects can be explained by assuming that Ni^{2+} and Ca^{2+} compete for the same membrane sites. The available data are not sufficient to determine the type or kinetics of competition. More extensive data from the giant barnacle muscle allow a more complete comparison based on the maximal rate of rise of the action potential, which is known to be Ca^{2+}-dependent. The order of binding[9] is: La, UO_2, Zn, Co, Fe, Mn, Ni, Ca, Mg, and Sr. The action potentials of nonmyelinated fibers from the vagus of the cat are likewise prolonged by nickel, as is the action potential of large nonmyelinated lobster axons.[50] The study of Blaustein and Goldman[50] contains voltage-clamp data on Na^+ and K^+ fluxes and the influence of Ni^{2+} and Ca^{2+} on them. Stretch receptors from crayfish show the same prolonged action potential.[689] The action potential of squid giant axon is not affected by nickel, either applied to the surface or injected internally.[559]

In Ni^{2+} solutions, the threshold for action-potential production is increased in the nerves studied by Khodorov and Belyayev,[300,301] Blaustein and Goldman,[50] and Hille.[247] Voltage-clamp data from myelinated frog nerve fibers show that Ni^{2+} causes the same shift in soluble sodium versus membrane potassium as does 5mM Ca^{2+}, although Ni^{2+} appears to do more than just replace Ca^{2+}.[247] The same 1:5 ratio has been found in lobster nerve.[50] This increase in threshold leads to an antagonism of the effects of tetrodotoxin and procaine by Ni^{2+}.[301]

Contractile Tissue

In muscle, calcium has two major roles: stabilizing the surface membrane and activating the contractile proteins. Nickel, in millimolar concentrations, will replace calcium at the surface membrane of frog skeletal muscle[165] to prevent the effect of Ca^{2+}-free Ringer's solution, depolarization,[108] and the resetting of the mechanism that releases intracellular Ca^{2+}.[279] With Ni^{2+}, a muscle will continue to twitch or give contractions for 4–6 h, instead of the 20–30 min with Ca-free Ringer's solution. At the end of 4 h, the muscle in Ni^{2+} Ringer's solution gradually fails to contract, whereas the control muscle in Ca Ringer's is still active. Ca^{2+} leaves a muscle bathed in Ni^{2+} Ringer's,[107] but the Ni^{2+} that enters cannot activate the contractile proteins;[155] hence, contraction fails. Neither does Ni^{2+} activate the skinned-fiber preparation (Podolsky, personal communication quoted by Edwards, Lorkovic, and Weber[134]). Resting Ni^{2+} fluxes are very similar in time constant and compartment size to Ca^{2+} fluxes, but there is no increase in Ni^{2+} influx with contracture.[155] Ni^{2+} also causes an internal rearrangement of Ca^{2+}, shifting it to the compartment that activates the contractile proteins.[107]

The duration of the surface action potential of skeletal muscle is increased by Ni^{2+},[155] which leads to a potentiation of the twitch[517] in both duration and amplitude, as well as a lowering of the tetanus fusion frequency. The observed increased duration of the active state is presumably related to these effects. A similar increased duration of both the action potential and the active state is observed in the replacement of Cl^- by such anions as NO_3^- and I^-.[245]

The effect of nickel on heart muscle is also twofold; both membrane action potential and contractile force are affected. Ni^{2+} lengthens the plateau phase of the action potential of dog ventricle and Purkinje fibers,[307] of frog ventricle, and of guinea pig papillary muscle.[293] The action potential of rat atrium is shortened by Ni^{2+}.[306] In most of the relevant studies, millimolar concentrations of Ni^{2+} were added to the Ca-containing perfusion fluid. The threshold for the effect in dog heart is 0.5×10^{-4} *M* nickel chloride. Ni^{2+} has been reported to reduce the contractile force of both atrium and ventricle.[293,306] Kohlhardt *et al.*[311] have found that Ni^{2+} selectively inhibits transmembrane calcium conductivity of muscle fibers in the cat myocardium.

Humans exposed to nickel carbonyl have also shown the effects of nickel on the myocardium, as reflected in the ECG. The S-T segment of the ECG, which corresponds to the plateau phase of the intracellular action potential, is increased.[142,655]

Information on Ni^{2+} interaction with smooth muscle is much more limited. When millimolar quantities of Ni^{2+} are substituted for Ca in guinea pig *Taenia coli*, the long-lasting tonic response to increased K^+ remains, but the phasic portion is thought to depend on conducted action potentials. Even if Ni^{2+} is applied in the presence of Ca, the phasic response is inhibited.[269] In guinea pig uterus, Ni^{2+} stimulates contraction and increased alkaline phosphatase activity.[99]

In other contractile systems, Ni^{2+} causes gross interference with the mitotic spindle apparatus in cultured rat embryo limb muscle cells. Older cultures are less affected by Ni^{2+}; no report on their contractibility was included.[625] Ni^{2+} completely inhibits the ciliary reversal response in paramecia.[425]

Neuromuscular Transmission

Nickel has several interesting effects at the neuromuscular junction, although none of them results in blocked transmission. The prolongation of the axonal action potential by Ni^{2+} increases the duration of the presynaptic potential, which in turn delays and prolongs the release of transmitter.[44] Ni^{2+} also decreases the number of acetylcholine "quanta" released by a single action potential.[364] This reduction is not a direct consequence of action-potential prolongation, inasmuch as other ions ($UO_2{}^{2+}$, TEA^+) that prolong the action potential do not decrease the quantal content.[365] In decreasing the quantal content, Ni^{2+} appears to be acting like Mg^{2+}, competing with Ca^{2+} for the active site that controls both quantal content and miniature end-plate potential frequency.

Central Nervous System

Reports of the action of Ni^{2+} on the central nervous system are rare, both in the literature and in the memories of several experienced neurologists. Nickel chloride (0.15 g/kg, intravenously) is reported to cause a breakdown in the blood–brain barrier in rats.[671] Metallic nickel pellets implanted in monkey cortex give rise to extensive epileptic seizures and later death in status epilepticus.[85] These nickel pellets, as opposed to most metal pellets, cause a soft necrotic lesion many times the size of the pellets.

4

Nickel Toxicity

ANIMAL TOXICITY OF NICKEL AND ITS COMPOUNDS

Studies conducted at the turn of the century (see Chapter 1) indicated that large oral doses of nickel salts resulted in gastrointestinal irritation with vomiting and diarrhea. Nickel metal is relatively nontoxic; dogs tolerated 1-3 g/kg by oral administration without any obvious effects.[571] Dogs and cats tolerated daily doses of 4-12 mg/kg for 200 days with no ill effects.[571] The inorganic nickel salts are well tolerated by rodents when administered orally. Nickel carbonate, nickel soaps, and nickel catalyst (for example, Raney nickel) administered in the diet of young rats at 250, 500, and 1,000 ppm for 8 weeks did not have any significant effect on growth rate.[480] Approximately 90% of the nickel given as nickel soaps or nickel catalyst was found in the feces; less than 1% was excreted in the urine. When given as nickel carbonate, 74% of the nickel was excreted in the feces and 1.6% in the urine. Retention of nickel in the tissues was highest in the group given nickel carbonate. The highest tissue concentrations, 140-360 ppm, were found in bone; other tissues contained 10-50 ppm. In a later experiment, nickel catalyst was fed in the diet at 250 ppm for 16 months.[481] Again, there was no effect on the general condition or growth of the rats. Tissue nickel content progressively increased up to 8 months, then declined in spite of continued intake. Once it was withdrawn from the diet, nickel was not detected in feces after 20 days or in urine after 40 days.

Mice tolerated nickel acetate in their drinking water at 5 ppm over their lifetime. In terms of growth, survival, and tumor incidence, nickel in this form was judged to be inert.[529,533]

Phatak and Patwardhan[480] fed monkeys (*Macaca sinicus*) diets containing nickel at 250, 500, and 1,000 ppm for 24 weeks. As in the rat studies conducted by these investigators, nickel was incorporated in the diet in three forms—nickel catalyst, nickel soap, and nickel carbonate. In terms of growth, behavior, and hematologic characteristics (hemoglobin concentration and red-cell and white-cell counts), these concentrations did not produce any deleterious effects. No analyses of nickel content of tissues or organ histopathology were reported.

Toxic effects were observed in male Holstein calves given nickel carbonate, $NiCO_3$, via the diet over an 8-week period.[453] A normal body-weight gain was observed at the lowest concentration, 62.5 ppm. At 250 ppm, food intake and growth were slightly reduced; and at 1,000 ppm, they were markedly reduced. The authors stress that, in spite of the weight loss, the calves did not appear emaciated, but appeared to be younger than the others. In the recovery period, the growth rate of those given the 1,000-ppm diet was equal to that of the others. Relative to body weight, fresh weights of lung, heart, spleen, liver, gall bladder, kidney, brain, and testis were not affected. Some kidney abnormalities were observed in all groups, but pyelonephritis was observed only in the high-dosage group.

When chicks were fed diets containing nickel, as either the sulfate or the acetate, significant decrease in growth was observed at 700 ppm and above.[694] No significant differences were observed between the two forms of nickel. Body weights were normal up to 300 ppm, but growth was significantly reduced between 300 and 700 ppm and further reduced at 900–1,300 ppm. Nitrogen retention decreased progressively above 500 ppm. Because the higher dosages reduced food consumption, a paired feeding study was performed at 1,100 ppm. When food consumption was equalized, nickel did not affect growth, but nitrogen retention was decreased.

Gordynya[204] administered nickel chloride to young male rabbits orally at 500 μg/day for 5 months. He found that the nickel chloride decreased liver glycogen, increased muscle glycogen, and produced prolonged hyperglycemia after a galactose load.

When administered intravenously or subcutaneously, the nickel salts are highly toxic. Nickel chloride or colloidal nickel in single intravenous doses of 10–20 mg/kg was lethal in dogs.[571] Gastroenteritis, tremor, and paralysis were observed after intravenous administration of lethal doses. The lethal doses of nickel oxide were 8 mg/kg in cats and 6 mg/kg in dogs.[63] The LD_{50} of nickel sulfate in the guinea pig after intravenous administration was 62 mg/kg.[581] Additional data on parenteral LD_{50} for various nickel compounds are included in Tables 4-1, 4-2, and 4-3.

In contrast with oral administration, after which 90% or more of the ingested nickel is excreted in the feces, parenterally administered nickel is excreted mostly in the urine. After single small doses (0.74 or 1.47 μg) of nickel-63 in the rat, 61% was excreted in the urine and only 5.9% in the feces within 72 h.[552] All radioactivity had disappeared from whole blood and plasma within 48 h. After 72 h, significant amounts of nickel-63 were found only in the kidneys. After shorter intervals, the distribution of nickel-63 correlated well with the blood volume of the specific organ studied; this suggests that the distribution of nickel depended directly on blood volume. Studies of the distribution and excretion of divalent nickel after parenteral administration to rodents have also been reported.[83,250,455,619,670,688]

Onkelinx *et al.*[455] studied the kinetics of nickel-63 metabolism in rats and rabbits after a single intravenous injection of $^{63}NiCl_2$. In both species, nickel-63 was rapidly cleared from plasma or serum during the first 2 days after the injection, and it disappeared at a much lower rate during days 3–7. Urinary excretion of nickel-63 averaged 78% of the administered dose during the first day after the injection in rabbits and 78% of the dose during 3 days after the injection in rats. Measurements of nickel-63 distribution and excretion in both species suggested that nickel-63 is diluted within a volume composed of two compartments and that it is eliminated by first-order kinetics. Onkelinx *et al.*[455] proposed a mathematical model that permits the description of $^{63}Ni(II)$ metabolism in quantitative terms. The two-compartment model was tested and verified by its ability to predict concentrations of nickel-63 in serum or plasma of animals that received continuous infusions or repeated daily injections of $^{63}NiCl_2$.

Ceresa[79] reported that nickel administered to guinea pigs by subcutaneous injection was eliminated primarily by the kidneys. After 120 days of administration, nickel was present in all organs studied. Berenshteyen and Shifrina, cited by Gordynya,[204] found that parenteral injection of nickelous chloride produced either an increase or a decrease in blood glucose, depending on dosage. Clary and Vignati[87] administered nickelous chloride intraperitoneally to rats in nickel doses ranging from 10 to 80 mg/kg of body weight and observed the immediate development of hyperglycemia. The hyperglycemia was prevented by simultane-

TABLE 4-1 Toxicity of Inorganic Nickel Compounds in Animals[a]

Compound	Formula	Mol Wt	Route of Administration[b]	Animal	Toxicity Data[c]
Nickel	Ni	58.71	ims	Rat	TDLO = 110 mg/kg
			ims	Mouse	TDLO = 800 mg/kg
			ivn	Dog	LDLO = 10 mg/kg
			orl	Guinea Pig	LDLO = 5 mg/kg
Nickel acetate	$Ni(C_2H_3O_2)_2$	202.84	ims	Rat	TDLO = 420 mg/kg
Nickel carbonyl	$Ni(CO)_4$	170.75	inl	Rat	LC_{50} = 240 mg/m^3
			ivn	Rat	LD_{50} = 22 mg/kg
			ipr	Rat	LD_{50} = 13 mg/kg
Nickel chloride	$NiCl_2$	129.61	ivn	Dog	LDLO = 10 mg/kg
			ipr	Rat	LDLO = 6.5 mg/kg
			ipr	Rat	LD_{50} = 11 mg/kg
			ipr	Rat	LD_{100} = 17 mg/kg
Nickel fluoborate	$Ni(BF_4)_2$	232.35	ihl	Mouse	LDLO = 0.53 mg/liter
			orl	Rat	LDLO = 500 mg/kg

Nickel fluoride	NiF_2	96.71	ivn	Mouse	LD_{50} = 130 mg/kg
Nickel fluosilicate	$NiSiF_6 \cdot 6H_2O$	228.90	orl	Rat	LDLO = 100 mg/kg
Nickel nitrate	$Ni(NO_3)_2$	210.80	orl	Rat	LD_{50} = 1,620 mg/kg
Nickel oxide	NiO	74.71	ims	Rat	TDLO = 180 mg/kg
			ims	Mouse	TDLO = 400 mg/kg
			ivn	Dog	LDLO = 7 mg/kg
Nickel perchlorate	–	–	ipr	Mouse	TDLO = 100 mg/kg
Nickel subsulfide[d]	Ni_3S_2	240.25	ims	Rat	TDLO = 90 mg/kg
			ims	Mouse	TDLO = 200 mg/kg
Nickel sulfamate	–	–	ipr	Mouse	LDLO = 250 mg/kg
Nickel sulfate	$NiSO_4 \cdot 6H_2O$	262.89	scu	Dog	LDLO = 500 mg/kg
			scu	Guinea Pig	LDLO = 62 mg/kg
			scu	Rabbit	LDLO = 500 mg/kg

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[a] Derived from Christensen[84] and F. W. Sunderman, Jr. (personal communication).

[b] ihl = inhalation; ims = intramuscular; ipr = intraperitoneal; ivn = intravenous; orl = oral; scu = subcutaneous.

[c] LC_{50} = lethal concentration (50% killed); LD_{50} = lethal dose (50% killed); LD_{100} = lethal dose (100% killed); LDLO = lowest published lethal dose; TDLO = lowest published toxic dose.

[d] Toxic effects are carcinogenic.

TABLE 4-2 Toxicities of Some Nickel Complexes and Nickel Salts in Experimental Animals

Authors	Date	Compound	Route of Administration	Animal	LD_{50}
Franz[166]	1962	Nickel chloride hexahydrate	Intraperitoneal	Mouse	48 mg/kg
Nofre *et al.*[445]	1963	Nickel-disodium-EDTA[a]	Intraperitoneal	Mouse	600 mg/kg
		Nickel sulfate heptahydrate	Intraperitoneal	Mouse	38 mg/kg
Joesten and Hill[280]	1966	Nickel perchlorate-3 OMPA[b]	Intraperitoneal	Mouse	15 mg/kg
		Nickel perchlorate hexahydrate	Intraperitoneal	Mouse	100 mg/kg
Haro *et al.*[222]	1968	Nickelocene[c]	Intraperitoneal	Mouse	86 mg/kg
		Nickel acetate	Intraperitoneal	Mouse	32 mg/kg
		Nickelocene	Intraperitoneal	Rat	50 mg/kg
		Nickel acetate	Intraperitoneal	Rat	23 mg/kg
		Nickelocene	Oral	Mouse	600 mg/kg
		Nickel acetate	Oral	Mouse	420 mg/kg
		Nickelocene	Oral	Rat	500 mg/kg
		Nickel acetate	Oral	Rat	350 mg/kg
Innes *et al.*[271]	1969	Ni-DBDTC[d]	Oral	Mouse	(MTD = 0.1 mg[e])

[a] EDTA = ethylenediaminetetraacetate.
[b] OMPA = octamethylpyrophosphoramide.
[c] Nickel dicyclopentadiene.
[d] DBDTC = dibutyldithiocarbamate.
[e] MTD (maximal tolerated dose) = maximal oral dose resulting in zero mortality after 19 daily doses.

TABLE 4-3 Toxicity Studies of Nickel Carbonyl in Experimental Animals

Authors	Date	Route of Administration	Animal	Lethal Dose
McKendrick and Snodgrass[388]	1890	Subcutaneous	Rabbit	LD_{100} = 25 mg/kg
Hanriot and Richet[218]	1891	Intravenous	Rabbit	LD_{100} = 40 mg/kg
			Dog	LD_{100} = 33 mg/kg
Langlois[325]	1891	Intravenous	Dog	LD_{100} = 33 mg/kg
Vahlen[661]	1902	Subcutaneous	Dog	LD_{100} = 50 mg/kg
Armit[14]	1908	Inhalation	Rabbit	LD_{80} = 1.4 mg/liter for 50 min
			Cat	LD_{80} = 3.0 mg/liter for 75 min
			Dog	LD_{80} = 2.7 mg/liter for 75 min
Garland[185]	1933	Inhalation	Mouse	LD_{80} = 0.17 mg/liter for 5 min
Barnes and Denz[26]	1951	Inhalation	Rat	LD_{80} = 0.9 mg/liter for 30 min
Kincaid *et al.*[305]	1953	Inhalation	Mouse	LD_{50} = 0.067 mg/liter for 30 min
			Rat	LD_{50} = 0.24 mg/liter for 30 min
			Cat	LD_{50} = 0.19 mg/liter for 30 min
Sanotskii[519]	1955	Inhalation	Mouse	LD_{100} = 0.2 mg/liter for 120 min
			Mouse	LD_{0} = 0.01 mg/liter for 120 min
Ghiringhelli[190]	1957	Inhalation	Rat	LD_{100} = 0.3 mg/liter for 20 min
			Rat	LD_{50} = 0.1 mg/liter for 20 min
West and Sunderman[707]	1958	Inhalation	Mouse	LD_{80} = 0.048 mg/liter for 30 min
			Rat	LD_{65} = 0.50 mg/liter for 30 min
Sunderman *et al.*[591]	1961	Inhalation	Dog	LD_{90} = 2.5 mg/liter for 30 min
Sunderman[583]	1964	Inhalation	Rat	LD_{30} = 0.51 mg/liter for 30 min
Hackett and Sunderman[213]	1967	Intravenous	Rat	LD_{50} = 65 mg/kg
		Subcutaneous	Rat	LD_{50} = 61 mg/kg
		Intraperitoneal	Rat	LD_{50} = 38 mg/kg
		Inhalation	Rat	LD_{50} = 0.58 mg/liter for 15 min
Sanina[518]	1968	Inhalation	Mouse	LD_{100} = 0.1 mg/liter for 120 min LD_{0} = 0.01 mg/liter for 120 min

TABLE 4-4 Distribution of ^{63}Ni in Tissues of Rodents after Injection of $^{63}NiCl_2$

Authors	Animal	Dosage[a]	Relative Distribution of ^{63}Ni
Wase *et al.*[688]	Mouse (N = 8)	6.2 mg/kg (one intraperitoneal injection)	kidney ≫ lung ≫ plasma > liver > erythrocyte > spleen > bladder > heart > brain > carcass (muscle, bone, and fat)
Smith and Hackley[552]	Rat (N = 4)	6/7 μg/kg (one intravenous injection)	kidney ≫ lung > adrenal > ovary > heart = gastrointestinal tract > skin > eye > pancreas > spleen = liver > muscle > teeth > bone > brain = fat
Clary[86]	Guinea Pig (N = 6)	1 mg/kg (subcutaneously for 5 days)	kidney ≫ pituitary ≫ lung ≫ liver > spleen > heart > adrenal > testis > pancreas > medulla oblongata = cerebrum = cerebellum
Parker and Sunderman[463]	Rabbit (N = 3)	240 μg/kg (one intravenous injection)	kidney ≫ pituitary > serum > whole blood > skin > lung > heart > testis > pancreas > adrenal > duodenum > bone > spleen > liver > muscle ≫ spinal cord > cerebellum > medulla oblongata = hypothalamus
	Rabbit (N = 4)	4.5 μg/kg (intravenously for 34–38 days)[b]	kidney ≫ pituitary > spleen > lung > skin > testis > serum = pancreas = adrenal > sclerae duodenum = liver > whole blood > heart > bone > iris > muscle > cornea = cerebellum = hypothalamus > medulla oblongata > spinal cord > retina > lens > vitreous humor

[a] Unless otherwise noted, animals were killed 2 h after the last injection of $^{63}NiCl_2$.
[b] Animals were killed 24 h after the last injection of $^{63}NiCl_2$.

ous administration of insulin. Wase *et al.*,[688] Smith and Hackley,[552] Clary,[86] and Parker and Sunderman[463] have measured the relative distributions of ^{63}Ni in tissues of rodents after injections of $^{63}NiCl_2$. There is substantial agreement between the results of these investigations (Table 4-4). In all the studies, the highest concentrations of ^{63}Ni were found in kidneys. Lungs were also generally very rich in ^{63}Ni. Parker and Sunderman[463] observed a striking localization of ^{63}Ni in the pituitary of the rabbit. Of the various tissues studied, the concentrations of ^{63}Ni in the pituitary were second only to those in the kidneys. This observation was independently confirmed by Clary[86] in his investigation of the distribution of ^{63}Ni in tissues of guinea pigs. The finding that ^{63}Ni is particularly localized in the pituitary may have physiologic significance, in view of the reports by LaBella *et al.*[319,320] that Ni(II) depression of prolactin release was observed under basal conditions, as well as in such circumstances as cold exposure, in which there is augmented secretion of prolactin. Furthermore, LaBella *et al.* have found that intravenous administration of Ni(II) as $NiCl_2$ to chlorpromazine-treated male rats in nickel dosages of 300–600 μg/kg of body weight results in a 40% decrease in serum prolactin content 30 min after the injection. Although LaBella *et al.* have not identified the exact site of action of Ni(II) on prolactin secretion, they have suggested that Ni(II) may exert a direct, specific inhibitory action on prolactin-secreting cells in the anterior pituitary.

Studies of the effects of inhalation of nickel compounds on experimental animals have been performed primarily with nickel carbonyl and were concerned mainly with carcinogenesis. Bingham *et al.*[49] have recently investigated the pulmonary response to inhalation of nickel oxide and nickelous chloride. They observed that nickel oxide markedly increased the number of alveolar macrophages and that nickelic chloride increased the viscosity of pulmonary washings. They stated that, "in view of the experimental results obtained with NiO and $NiCl_2$, the level of the current TLV for nickel (1,000 μg/cu meter) should be scrutinized. The data obtained in these experiments at levels of approximately one tenth of the current TLV suggest that 1,000 μg/cu meter may be too high. Certainly additional experiments are required to make a scientifically sound judgment concerning the validity of the current TLV." These topics are discussed in the final section of this chapter and in Chapter 6.

Although more than 180 organonickel compounds and nickel complexes are commercially available in the United States, toxicity studies have been reported for only a few of them (Tables 4-2 and 4-3). In the investigations of Nofre *et al.*,[445] Joesten and Hill,[280] and Haro *et al.*,[222] the acute toxicities of some nickel complexes were compared with those of related nickel salts. As indicated in Table 4-2, the LD_{50} for nickel–disodium–EDTA and nickelocene was greater than that for nickel sulfate, nickel acetate, and nickel chloride, whereas the LD_{50} for the nickel perchlorate complex of octamethylpyrophosphoramide was approximately one-seventh of that for nickel perchlorate. Little is known about the mechanisms of toxicity of any nickel pi-complexes, except nickel carbonyl. Buu-Hoi *et al.*[70] demonstrated that intraperitoneal administration of nickelocene to rats (20–50 mg/kg) prolonged zoxazolamine-induced paralysis and potentiated anticoagulation induced by ethyl biscoumacetate. They concluded that these effects were probably attributable to nickelocene inhibition of hepatic drug metabolism. Chen *et al.*[83] measured urinary excretion of nickel after intramuscular administration of nickelocene and nickel acetate to rats. With both these compounds, approximately 95% of the administered dose of nickel was recovered in the urine within 14 days.

Owing to its industrial importance and widespread usage, there have been numerous investigations of the toxicity of nickel carbonyl (Table 4-3). Nickel carbonyl is a colorless, volatile liquid (boiling point, 43 C) that is particularly dangerous if inhaled. Armit[14] and Garland[185] demonstrated that the acute inhalation toxicity of nickel carbonyl is approximately 100 times greater than that of carbon monoxide. The signs and symptoms that occur in animals from 12 h to 5 days after exposure to nickel carbonyl include dyspnea, tachypnea, cyanosis, fever, apathy, anorexia, vomiting, diarrhea, and, occasionally, hindlimb paralysis. Generalized convulsions are frequently a terminal event.

Studies of the pathologic lesions that develop in experimental animals after acute exposure to nickel carbonyl are summarized in Table 4-5. The pulmonary parenchyma has been found to be the target tissue for nickel carbonyl in all species tested, regardless of route of administration. Within an hour after exposure, edema develops in the interstitium of the alveolar septa. By 24 h, polymorphonuclear leukocytes accumulate in the peribronchiolar and alveolar septal interstitium and, to a lesser degree, within the alveolar spaces. There is proliferation and hyperplasia of the bronchiolar epithelium and of the alveolar lining cells. During the second to fifth days after exposure, there is severe intra-alveolar edema with focal hemorrhage and pronounced distortions of the membranous and granular pneumocytes that line the alveoli. The nuclei of these cells become enlarged and contain numerous dense nucleoli; atypical mitoses are frequent. The cytoplasm of these cells develops prominent arrays of rough endoplasmic reticulum, as well as numerous cisternal structures and multivesicular bodies. Death usually occurs during the third to fifth days. In surviving animals, during the sixth to tenth days after exposure, the cytologic alterations regress toward normal, and fibroblastic proliferation occurs within the interstitium of the alveolar wall. Foci of adenomatous transformation also become apparent within the pulmonary parenchyma. From 14 to 21 days after exposure, the pulmonary parenchyma is essentially normal, except for interstitial fibrosis.

Pathologic reactions in other organs after acute exposure of animals to nickel carbonyl are less severe than the pulmonary lesions. However, focal hemorrhage, congestion, edema, hydropic degeneration, mild inflammation, and vacuolization have been reported in brain, liver, kidneys, adrenals, spleen, and pancreas. In hepatic parenchymal cells, diffuse dilatation of rough endoplasmic reticulum is the most prominent and consistent ultrastructural abnormality. Nucleolar alterations also develop within hepatocytes during the period from 2 to 24 h after exposure to nickel carbonyl.

There have been numerous investigations of the distribution of nickel in various organs and of the excretion of nickel in urine and feces after exposure of experimental animals to nickel carbonyl (Table 4-6). Controversy regarding the rapidity of metabolic decomposition of nickel carbonyl and regarding the metabolic fate of the carbonyl moiety has been resolved by studies using [^{63}Ni] nickel carbonyl and [^{14}C] nickel carbonyl[292,619] and by gas chromatographic measurements of nickel carbonyl in blood and breath.[618] These investigations have demonstrated that nickel carbonyl can pass across the alveolar membrane in either direction without metabolic alteration. Nickel carbonyl that is inhaled or injected does not immediately decompose. In the rat, approximately 36% of an injected dose of nickel carbonyl is excreted in the expired breath within 4 h. Thus, the lung is a major excretory organ for nickel carbonyl. The remainder of the nickel carbonyl slowly undergoes intracellular dissociation within red cells and other tissues to liberate nickel (Ni^0) and carbon monoxide. The carbon monoxide becomes bound to hemoglobin and is transported to the lungs, where it is also exhaled. Approximately 49% of the carbonyl moiety of an injected dose of nickel carbonyl is expired as carbon monoxide and 1% is expired as carbon dioxide within 6 h. In the rat, carbon monoxide saturation of hemoglobin reaches a peak during the second hour, and thereafter the carbon monoxide saturation of hemoglobin decreases exponentially with a half-life of approximately 90 min, paralleling the exhalation rate of carbon monoxide. The nickel (Ni^0) that is released from nickel carbonyl is oxidized intracellularly to Ni(II) and is released into the blood serum. The Ni(II) becomes bound predominantly to serum albumin and

TABLE 4-5 Pathologic Lesions after Acute Exposure of Experimental Animals to Nickel Carbonyl

Authors	Date	Route of Administration	Animal	Dose	Observation Period after Exposure	Observations
Armit[14]	1908	Inhalation	Rabbit	1.4 mg/liter for 50 min	1–5 days	*Lungs:* intra-alveolar hemorrhage, edema, and exudate and alveolar cell degeneration; *adrenals:* hemorrhages; *brain:* perivascular leukocytosis and neuronal degeneration
Barnes and Denz[26]	1951	Inhalation	Rat	0.9 mg/liter for 30 min	2 h–1 year	*Lungs:* at 2–12 h, capillary congestion and interstitial edema; at 1–3 days, massive intra-alveolar edema; at 4–10 days, pulmonary consolidation and interstitial fibrosis
Kincaid *et al.*[105]	1953	Inhalation	Rat	0.24 mg/liter for 30 min	0.2 h–6 days	*Lungs:* at 1 h, pulmonary congestion and edema; at 12 h–6 days, interstitial pneumonitis with focal atelectasis and necrosis, and peribronchial congestion; *liver, spleen, kidneys, and pancreas:* parenchymal cellular degeneration with focal necrosis

Sunderman *et al.*[591]	1961	Inhalation	Rat Dog	1.0 mg/liter for 30 min	1–6 days 1–7 days	*Lungs:* at 1–2 days, intra-alveolar edema and swelling of alveolar lining cells; at 3–5 days, inflammation, atelectasis, and interstitial fibroblastic proliferation; *kidneys and adrenals:* hyperemia and hemorrhage
Hackett and Sunderman[213]	1967	Intravenous	Rat	65 mg/kg	0.1 h–21 days	*Lungs:* at 1–4 h, perivascular edema; at 2–5 days, severe pneumonitis with intra-alveolar edema, hemorrhage, subpleural consolidation, hypertrophy and hyperplasia of alveolar lining cells, and focal adenomatous proliferation; at 8 days, interstitial fibroblastic proliferation; *liver, kidneys, and adrenals:* congestion, vacuolization, and edema
Hackett and Sunderman[215]	1968	Intravenous	Rat	65 mg/kg	0.5 h–8 days	*Lungs:* ultrastructural alterations, including edema of endothelial cells at 6 h and massive hypertrophy of membranous and granular pneumocytes at 2–6 days
Hackett and Sunderman[214]	1969	Intravenous	Rat	65 mg/kg	0.5 h–6 days	*Liver:* ultrastructural alterations of hepatocytes including nucleolar distortions at 2–24 h, dilatation of rough endoplasmic reticulum at 1–4 days, and cytoplasmic inclusion bodies at 4–6 days

TABLE 4-6 Studies of Nickel Metabolism After Exposure of Experimental Animals to Nickel Carbonyl

Authors	Date	Route of Administration	Animal	Observations
Hanriot and Richet[218]	1891	Intravenous	Dog and rabbit	Nickel carbonyl did not immediately decompose in blood
Langlois[325]	1891	Intravenous	Dog and rabbit	Nickel carbonyl may combine with hemoglobin
Vahlen[661]	1902	Intravenous	Dog	Carboxyhemoglobins demonstrated in blood by spectroscopy
Armit[14]	1908	Inhalation	Dog, cat, and rabbit	Nickel found in lungs, brain, kidneys, adrenals, and blood; excretion of nickel in urine (75%) and feces (25%); suggested nickel carbonyl is metabolized to $2NiCO_3 \cdot 3Ni(OH)_2 \cdot 4H_2O$, and that carbon monoxide poisoning is not a major factor
Barnes and Denz[26]	1951	Inhalation	Rat	Nickel found rapidly mobilized from lungs, liver, and brain after exposure
Sunderman *et al.*[589]	1957	Inhalation	Rat	Increased nickel in liver and kidneys after acute and chronic exposure
Tedeschi and Sunderman[616]	1957	Inhalation	Dog	Inhaled nickel rapidly excreted in urine (90%) and feces (10%)
Ghiringhelli and Agamennone[191]	1957	Inhalation	Rat	Rapid mobilization of nickel from lungs, liver, kidneys, and brain during 48 h after exposure

Sunderman *et al.*[591]	1961	Inhalation	Rat and dog	Maximal excretion of nickel in urine during 24 h after exposure; increased urinary nickel excretion throughout first week
Sunderman[607]	1963	Inhalation	Rat	Nickel binding to RNA from lungs and liver
Sunderman and Sunderman[620]	1963	Inhalation	Rat	Nickel concentrations increased in microsomal and supernatant fractions of lung and liver hemogenates
Sunderman[583]	1964	Inhalation	Rat	Nickel in supernatant fraction from lung and liver homogenates partially bound to macromolecular components
Sunderman and Selin[619]	1968	Intravenous and inhalation	Rat	At 24 h after inhalation of [^{63}Ni] nickel carbonyl, partition of body burden of nickel-63 is: viscera, 50%; muscle and fat, 30%; bone and connective tissue, 16%; and neural tissue, 4%; in lung and liver, nickel-63 is partially bound to RNA, DNA, and proteins
Sunderman *et al.*[618]	1968	Intravenous and inhalation	Rat	Gas chromatography demonstrated nickel carbonyl in blood after inhalation and in breath after intravenous injection; nickel carbonyl can cross alveolus without alteration
Kasprzak and Sunderman[292]	1969	Intravenous	Rat	After injection of [^{14}C] nickel carbonyl, 30% of carbon-14 is excreted in breath as [^{14}C] nickel carbonyl, and 50% as [^{14}C] carbon monoxide; [^{14}C] carboxyhemoglobin in blood reaches maximum 2 h after exposure
Mikheyev[405]	1971	Inhalation	Rabbit	Nickel rapidly mobilized from lungs, blood, and kidneys by exhalation (as nickel carbonyl) and in urine

to a lesser degree to ultrafiltrable nickel-binding substances that are present in the serum.

Nickel is rapidly cleared from the serum and excreted by the kidney. In the rat, an average of 23% of nickel, injected as nickel carbonyl, is excreted in the urine within 12 h and an average of 27% within 24 h. In contrast, only approximately 0.2% of injected nickel is excreted in the bile within 6 h. By the end of 4 days, an average of 38% of injected nickel can be recovered in breath, 31% in urine, and 2% in feces. Within homogenates of lung and liver, small portions of the intracellular nickel remain bound to DNA, RNA, and proteins. These apparent associations of nickel with nucleic acids and proteins should be interpreted cautiously, owing to possible artifactitious association or dissociation of nickel during the homogenization and extraction of these tissues.

Hackett and Sunderman[213,215] and Sunderman and Selin[619] have suggested that pathologic lesions in the lungs may result from damage produced during transit of nickel carbonyl across the alveolar epithelium, rather than from the toxicity of the small amount of nickel that remains in the lungs beyond 24 h after exposure. On this basis, the optimal therapy of acute nickel carbonyl poisoning would theoretically be to minimize the pulmonary exhalation of nickel carbonyl and to mobilize nickel carbonyl and carbon monoxide by extracorporeal gas exchange, using such an oxygenation apparatus as the Bramson membrane lung, which has been used successfully for prolonged extracorporeal oxygenation.[246] To date, this approach to therapy of nickel carbonyl poisoning has not been tested either in experimental animals or in man. There has, however, been considerable success in the therapeutic use of chelating drugs, as summarized in Table 4-7. Dimercaprol (BAL), thioctic acid, penicillamine, and sodium diethyldithiocarbamate (dithiocarb) have all been reported to be therapeutically beneficial in acute nickel carbonyl poisoning in experimental animals. Of these various chelating drugs, sodium diethyldithiocarbamate is by far the most effective therapeutic agent. Its antidotal efficacy against nickel carbonyl poisoning is illustrated by the animal experiments summarized in Table 4-8.[583]

Investigations that pertain to biochemical mechanisms of nickel carbonyl toxicity are summarized in Table 4-9. The observed effects of nickel carbonyl on enzyme induction and on RNA synthesis may be related to the mechanisms of nickel carcinogenesis and hence are discussed later in this report (see Chapter 6). Sanotskii[519] observed that body consumption of oxygen in mice was immediately diminished after exposure to nickel carbonyl and remained diminished for at least 3 days. Sunderman[597] found that ATP concentrations were increased in livers of rats that were killed 30 min or 24 h after injection of nickel carbonyl.

The effect of nickel carbonyl on hepatic ATP concentration may be mediated by Ni(II) inhibition of hepatic ATPase activity. Thus, Fedorchenko and Petrun[150] have reported that Ni(II) causes *in vitro* inhibition of ATPase activity in rat hepatic microsomes; Raff and Blum[488] have shown that *in vitro* addition of Ni(II) at 5×10^{-3} *M* inhibits ATPase activity of cilia of *Tetrahymena pyriformis*; and Mustafa *et al.*[423] observed that Ni(II) at 10^{-3} *M* inhibits ATPase activity of sheep alveolar macrophage cells. Moreover, Joó[283,284] has found that *in vivo* intraperitoneal administration of nickel chloride to rats at 25 mg/100 g of body weight 3–6 h before sacrifice abolishes ATPase activity in brain capillaries. Nickel has also been reported to cause reversible inactivation of ATP–creatine phosphotransferase activity at an *in vitro* concentration of 5×10^{-4} *M*.[456] A possible mechanism for Ni(II) inhibition of ATP-dependent enzymes has been elucidated by Sigel *et al.*[546] and Glassman *et al.*,[200] who have demonstrated that Ni(II) reacts *in vitro* with ATP to form a stable complex. Such a stable nickel–ATP complex might reversibly inhibit ATP utilization by saturating the ATP-binding sites of such enzymes as ATPase and creatine phosphotransferase. On the basis of these observations, Sunderman[597] has suggested that the acute toxicity of nickel carbonyl may derive, in part, from inhibition of ATP utilization.

TOXICITY OF NICKEL CARBONYL IN MAN*

Nickel carbonyl is the only organic nickel compound that has been recognized as a cause of human systemic toxicity. Nickel carbonyl, which was discovered by Mond *et al.*[414] in 1890, is a toxic, volatile liquid that is an intermediate product in the Mond process for nickel refining. It is also used for nickel plating in the electronics industry and as a catalyst in the petroleum, plastics, and rubber industries. The first severe cases of nickel carbonyl poisoning in workmen occurred in 1902, soon after industrial operations began at the Mond nickel refinery in Clydach, Wales.[255,433] As summarized in Table 4-10, there have been more than 250 reported cases of human poisoning after inhalation of nickel carbonyl. According to Vuopala *et al.*,[683] The International Nickel Company, Inc., in an unpublished report, has reviewed 354 severe cases of poisoning caused by inhalation of nickel carbonyl.

On the basis of personal observations of more than 200 workmen who

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* Nickel carcinogenesis is treated separately in Chapter 6.

TABLE 4-7 Studies of Chelation Therapy of Acute Nickel Carbonyl Poisoning in Experimental Animals

Authors	Date	Route of Administration of Nickel Carbonyl	Dose of Nickel Carbonyl	Animal	Chelating Agent[a]	Route of Administration of Chelating Agent	Total Dose of Chelating Agent	Observations
Barnes and Denz[26]	1951	Inhalation	0.9 mg/liter for 10–30 min	Rat	BAL	Subcutaneous	40–80 mg/kg	Prophylactic BAL (0.5 h before exposure) reduced mortality from nickel carbonyl; BAL therapy 0.5–4 h after exposure increased mortality
Kincaid *et al.*[305]	1953	Inhalation	0.2–0.6 mg/liter for 30 min	Rat	BAL	Intramuscular	23 mg/kg	BAL therapy during 3 days after nickel carbonyl significantly reduced mortality
Ghiringhelli[180]	1957	Inhalation	0.1–3 mg/liter for 20 min	Rat	BAL Thioctic acid	Subcutaneous Subcutaneous	24 mg/kg 80 mg/kg	BAL and thioctic acid both caused a twofold increase in LD_{50} from nickel carbonyl when administered for 4 days after exposure

West and Sunderman[706]	1958	Inhalation	0.06 mg/liter for 30 min	Mouse	CaEDTA	Intraperitoneal	40–500 mg/kg	CaEDTA had no therapeutic benefit when administered for 3 days after exposure to nickel carbonyl
West and Sunderman[707]	1958	Inhalation	0.05–0.3 mg/liter for 30 min	Mouse	DDC	Intraperitoneal	50–100 mg/kg	DDC provided complete protection against 5 × LD_{50} doses of nickel carbonyl in mice and rats; oral DDC in rats significantly reduced mortality; penicillamine was therapeutically effective in mice exposed to nickel carbonyl
			0.5–2.0 mg/liter for 30 min	Rat	DDC	Intraperitoneal or oral	50–100 mg/kg	
			0.06 mg/liter for 30 min	Mouse	Penicillamine	Intraperitoneal	200 mg/kg	
Sunderman[583]	1964	Inhalation	0.05–0.18 mg/liter for 30 min	Mouse	DDC	Intraperitoneal	50–100 mg/kg	DDC reduced mortality and increased excretion of nickel in urine and feces
			0.5–20 mg/liter for 30 min	Rat	DDC	Intraperitoneal or oral	50–100 mg/kg	

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[a] BAL, British antilewisite (2,3-dimercaprol); thioctic acid, δ-lipoic acid; CaEDTA, calcium-disodium ethylenediaminetetraacetic acid (edathamil calcium disodium); DDC, sodium diethyldithiocarbamate (dithiocarb); penicillamine, DL-β,β-dimethylcysteine.

TABLE 4-8 Antidotal Effect of Sodium Diethyldithiocarbamate (DDC) against Nickel Carbonyl Poisoning[a]

Animal	Inhalation Dose of Nickel Carbonyl, mg/liter for 30 min	Untreated Animals		Route of Administration of DDC[b]	Treated Animals	
		Total No.	No. Surviving 5 Days		Total No.	No. Surviving 5 Days
Mouse	0.05	30	6	Intraperitoneal	30	30
Mouse	0.06	30	0	Intraperitoneal	30	30
Mouse	0.08	390	2	Intraperitoneal	390	390
Mouse	0.12	30	0	Intraperitoneal	30	30
Mouse	0.18	30	0	Intraperitoneal	30	30
Rat	0.5	30	11	Intraperitoneal	30	30
Rat	0.8	30	6	Intraperitoneal	30	30
Rat	1.3	30	0	Intraperitoneal	30	30
Rat	2.0	30	0	Intraperitoneal	30	30
Rat	0.5	10	1	Oral	10	7
Rat	2.0	10	0	Oral	10	1

[a] Derived from Sunderman.[583]

[b] Intraperitoneal, 50 mg/kg immediately after exposure to nickel carbonyl; oral, 50 mg/kg by gastric intubation immediately after exposure to nickel carbonyl.

TABLE 4-9 Studies of Biochemical Mechanisms of Nickel Carbonyl Toxicity in Experimental Animals

Authors	Date	Route of Administration	Animal	Observations
Sanotskii[519]	1955	Inhalation	Mouse	Diminution of body oxygen consumption
Sunderman[599]	1967	Inhalation and intravenous	Rat	Inhibition of phenothiazine induction of benzopyrene hydroxylase in lungs and liver
Sunderman[602]	1967	Intravenous	Rat	Inhibition of cortisone induction of hepatic tryptophan pyrrolase
Sunderman[603]	1968	Intravenous	Rat	Inhibition of phenobarbital induction of hepatic cytochrome
Sunderman and Esfahani[610]	1968	Intravenous	Rat	Inhibition of RNA polymerase in hepatic nuclei
Beach and Sunderman[38]	1969	Intravenous	Rat	Inhibition of orotic acid incorporation into hepatic RNA
Beach and Sunderman[39]	1970	Intravenous	Rat	Inhibition of RNA synthesis by hepatic chromatin–RNA polymerase complex
Sunderman and Leibman[612]	1970	Intravenous	Rat	Inhibition of phenobarbital induction of aminopyrine demethylase in lungs and liver
Sunderman[596]	1970	Intravenous	Rat	Slight inhibition of leucine incorporation into hepatic microsomal proteins
Sunderman[597]	1971	Intravenous	Rat	Increased hepatic ATP concentration
Witschi[718]	1972	Intravenous	Rat	Inhibition of RNA synthesis in liver, but not in lungs

TABLE 4-10 Reported Cases of Nickel Carbonyl Poisoning in Man

Authors	Date	Country	No. Patients	No. Deaths	Days between Exposure and Death	Comments
Anon.[433]	1903	Wales	?	2	Several	Headache, giddiness, fever, and tachypnea in workmen in nickel carbonyl refinery
Mittasch[411]	1903	Germany	1	0	–	Author describes his own symptoms after accidental exposure
Armit[13]	1907	Wales	?	4	4–11	Classic description of clinical findings and gross pathology
Mott[421]	1907	Wales	2	2	?	Report of neuropathology in two of Armit's fatal cases
Brezina[67]	1929	Germany	6	1	?	Case reports (some cited by Kotzing)
Kotzing[317]	1933	Germany	5	0	–	Detailed case reports; one patient's symptoms mimic cholecystitis
Brandes[58]	1934	United States	1	1	7	Autopsy report, with identification of nickel in lungs and brain
Amor[10]	1935	Wales	1	1	?	Case report (cited by Bayer)
Bayer[36]	1939	Germany	15	2	3 and 5	Detailed case reports and pathologic descriptions
Carmichael[77]	1953	United States	1	0	–	Case report

Jones[282]	1973	United States	3	1	4	Case report; (DDC) therapy
Sunderman and Kincaid[588]	1954	United States	36	2	7 and 13	Dimercaprol (BAL) therapy; measurements of nickel in blood and urine
Sorinson[554]	1957	USSR	10	0	–	Summary of symptomatology and clinical course
Sunderman and Sunderman[594]	1958	United States	11	0	–	DDC therapy; measurements of urinary nickel
Morgan[417]	1960	Wales	23	0	–	Edathamil (CaEDTA) therapy; measurements of urinary nickel
Eisler and Rosmanith[142]	1960	Czechoslovakia	1	0	–	Case report, with ECG changes
Pilat *et al.*[483]	1964	Rumania	10	0	–	Protracted convalescence before return of normal respiratory function
Tseretili and Mandzhavidze[655]	1969	USSR	36	0	–	Describes clinical, ECG, with x-ray findings in severe cases
Nomoto and Sunderman[449]	1970	United States	3	0	–	Measurements of nickel in serum and urine in mild cases
Von Ludewigs and Theiss[680]	1970	Germany	46	2	3 and 4	Emphasizes correlation between clinical severity and urinary nickel
Vuopala *et al.*[683]	1970	Finland	25	0	–	Detailed clinical, laboratory, and pulmonary-function studies
Sunderman[585]	1971	United States	4	1	5	Protocol for therapy with DDC

suffered from nickel carbonyl poisoning, F. W. Sunderman, Sr.,[584] has summarized the clinical manifestations as follows:

> The initial symptoms in these patients usually include frontal headache, vertigo, nausea, vomiting and sometimes sternal and epigastric pain. In those patients who develop delayed reactions, constrictive pain in the chest is usually the first symptom. This is followed by cough, hyperpnea, cyanosis, occasionally gastrointestinal symptoms and a profound weakness. . . . The temperature in these patients seldom goes above 101°F and leukocytosis above 12,000 per cmm is infrequent. The pulse rate is usually increased but not in proportion to the increased respiratory rate. Physical signs compatible with pneumonitis or bronchopneumonia are elicited in the chest. Excepting for the pronounced weakness and hyperpnea, the physical findings and symptoms resemble those of a viral or influenzal pneumonia. Terminally, the patients frequently become delirious.

Sunderman[584] has emphasized that poisoning from inhalation of nickel carbonyl commonly goes unrecognized, because the "sooty" odor of nickel carbonyl vapor is difficult to detect; the initial symptoms are usually mild, nonspecific, and transitory; and the severe delayed symptoms often develop insidiously 12–36 h after exposure. Data on the relative incidences of various clinical manifestations of nickel carbonyl poisoning are listed in Table 4-11, based on the observations of Vuopala *et al.*[683] In addition to the clinical manifestations noted by Sunderman[584] and Vuopala *et al.*,[683] Tseretili and Mandzhavidze[655] observed hyperglycemia, glucosuria, hepatomegaly, and laboratory evidence of hepatic insufficiency in patients with severe nickel carbonyl poisoning. In subjects who recover from nickel carbonyl poisoning, convalescence is usually very protracted and is characterized particularly by fatigue on slight exertion. Frequently, 2–3 months are necessary before the patients feel that they are able to return to light work. Tseretili and Mandzhavidze[655] reported that x rays of patients a year after nickel carbonyl poisoning revealed pulmonary fibrosis.

The pathologic lesions reported in men who died after inhalation of nickel carbonyl are summarized in Table 4-12. The pathogenesis of the pulmonary lesions in man appears to be practically indistinguishable from that observed in experimental animals, as described in the preceding section. In the reported human cases, death has occurred from the third to the thirteenth day after exposure to nickel carbonyl. In most instances, death has been attributable primarily to respiratory failure, although cerebral edema and punctate cerebral hemorrhages may also have contributed in some patients. Mild to moderate parenchymal degeneration has also been observed in liver, kidneys, adrenal glands, and spleen. Measurements of nickel concentration in organs of men who

TABLE 4-11 Clinical Manifestations of Nickel Carbonyl Poisoning in 25 Men[a]

Immediate symptoms	Dyspnea (80%), fatigue (80%), nausea (76%), vertigo (44%), headache (36%), odor of "soot" in exhaled breath (36%), vomiting (24%), and insomnia and irritability (24%)
Latent period	In half of subjects, an asymptomatic interval between recovery from initial symptoms and onset of delayed symptoms
Delayed symptoms	Dyspnea with painful inspiration (80%), nonproductive cough (64%), muscular weakness (44%), substernal pain (44%), chilling sensations (32%), muscular pain (28%), sweating (24%), visual disturbances (12%), diarrhea (12%), abdominal pain (4%), muscle cramps (4%), and hypoesthesia in legs (4%)
Physical and x-ray findings	Tachypnea and tachycardia (80%), interstitial pneumonitis on x rays (60%), fever (40%), and cyanosis (36%)
Laboratory findings	Pulmonary-function tests consistent with interstitial lung disease (40%), increased serum glutamic pyruvic transaminase (36%), increased serum glutamic oxaloacetic transaminase (32%), and low arterial pO_2 (32%)
Clinical course	Interval before hospitalization: median, 2 days; range, 0–7 days. Duration of hospitalization: median, 6 days; range, 0–27 days. Interval before recovery: median, 38 days; range, 1–88 days. Symptoms that persisted for more than 3 weeks: fatigue (88%), exertional dyspnea (52%), muscular weakness (48%), headache (36%), abdominal pain (36%), muscular pain (32%), sweating (24%), visual disturbances (16%), and muscle cramps (8%).

[a] Based on observations of Vuopala *et al.*[683]

died from nickel carbonyl poisoning have been published,[36,58,585,588,680] and additional data are given in Chapter 3. In general, the highest nickel concentrations have been found in the lungs, and lower concentrations have been found in kidneys, liver, and brain.

Sunderman and Sunderman,[594] Von Ludewigs and Thiess,[680] and Vuopala *et al.*[683] have all reported close correlation between the clinical severity of acute nickel carbonyl poisoning and the urinary concentration of nickel during the first 3 days after exposure. Sunderman and Sunderman[594] have classified human exposure to nickel carbonyl as "mild" if the initial 8-h specimen of urine has a nickel concentration less than 10 μg/dl, "moderately severe" if the nickel concentration in the first 8-h collection is 10–50 μg/dl, and "severe" if the nickel concentration is greater than 50 μg/dl.

To date, there has been only one reported case of human disease that the authors attributed to chronic inhalation of low concentrations of nickel carbonyl (Sunderman and Sunderman[592]). The patient was a chemical engineer who developed asthma and Löffler's syndrome associated with exposure to inhaled nickel carbonyl. In addition to pulmonary roentgenographic changes and severe eosinophilia, which were

TABLE 4-12 Pathologic Lesions in Fatal Cases of Acute Nickel Carbonyl Poisoning in Man

Authors	Date	Observations
Armit[13]	1907	Gross pathologic findings in four men who died 4–11 days after exposure included hemorrhage in cerebral white matter and pulmonary hemorrhage and edema
Mott[421]	1907	Central nervous system pathology in two of Armit's cases included punctiform hemorrhages in white matter of cerebrum, cerebellum, brain stem, and spinal cord and focal degeneration of neural fibers in the cerebrum and of anterior horn cells in the spinal cord
Brandes[58]	1934	Autopsy of a man who died 7 days after exposure revealed pulmonary hemorrhage and edema, with marked swelling of alveolar lining cells and degeneration of bronchiolar epithelium; diffuse perivascular punctate hemorrhages in cerebral white matter and focal demyelinization of ganglion cells; and hyperemia and parenchymatous degeneration of liver, kidneys, and spleen
Bayer[36]	1939	Autopsy of two men who died 3 and 5 days after exposure showed diffuse swelling and desquamation of pulmonary alveolar epithelium, fibrinous intra-alveolar exudate, and cerebral, hepatic, and renal edema
Sunderman and Kincaid[588]	1954	Autopsy of a man who died 13 days after exposure demonstrated diffuse pulmonary interstitial fibrosis, pleural thickening and inflammation, and cerebral edema
Von Ludewigs and Thiess[680]	1970	Autopsy of two men who died 3 and 4 days after exposure revealed renal parenchymal damage and pulmonary inflammation and edema with focal hemorrhages
Smith and Kent (personal communication)	1971	Autopsy of a man who died 5 days after exposure showed diffuse pulmonary congestion and edema, degeneration and desquamation of alveolar epithelium with hyaline membrane formation, alveolar septal thickening with capillary dilatation and interstitial edema, mild centrilobular degeneration of hepatic parenchymal cells, and congestion of brain and kidneys
Jones[282]	1973	Autopsy of a man who died 4 days after exposure revealed pulmonary edema with intra-alveolar sanguineous exudate and marked cerebral edema; liver, adrenals, and kidneys were normal on gross and microscopic examination

typical of Löffler's syndrome, the patient exhibited eczematous dermatitis of the hands. Patch testing demonstrated marked cutaneous sensitivity to nickel. The patient recovered completely after removal of all contact with nickel, but died 5 years later from carcinoma of the lung (Sunderman, personal communication, 1972).

PREVENTION OF AND THERAPY FOR HUMAN EXPOSURE TO NICKEL CARBONYL

Reviews of the occupational hazards of nickel carbonyl have been published.[9,57,264,304,380,383,572,653] The prevention of accidental industrial exposure to nickel carbonyl is based primarily on careful plant design to ensure adequate ventilation and to safeguard against sources and causes of leakage of nickel carbonyl, continuous atmospheric monitoring and alarm systems to detect leakage of nickel carbonyl, systematic measurements of nickel in urine of workmen to detect otherwise unsuspected human exposure, and provision of respirators and protective clothing to safeguard workmen when an accident or breakdown does occur.

The analytic methods that have been described for detection of nickel carbonyl in air are listed in Table 4-13. Of the various techniques, the portable apparatus for air sampling and nickel analysis developed by Brief *et al.*[60] is the most practical for field use. The infrared-spectrophotometric method described by McDowell[387] is sensitive and relatively free from interferences, and it appears to be potentially applicable for continuous atmospheric monitoring. The gas-chromatographic method of Sunderman *et al.*[618] is the most specific and sensitive procedure, and it is especially suited for research purposes.

The American Industrial Hygiene Association[268] set the maximal atmospheric concentration for nickel carbonyl at 1 ppb (7 $\mu g/m^3$) for 8-h exposure. For short exposures, the American Industrial Hygiene Association[268] adopted the recommendation of Kincaid *et al.*,[304] who proposed a limit of 3 ppm for 30 min, on the basis of the assumption that the lethal atmospheric concentration of nickel carbonyl for man is 30 ppm for a 30-min exposure. The American Conference of Governmental Industrial Hygienists[7] set the threshold limit value for nickel carbonyl in industrial atmospheres at 1 ppb. Stokinger[572] proposed atmospheric limits for control of industrial exposure to nickel carbonyl, as given in Table 4-14. To aid in predicting risk of exposure to nickel carbonyl, Brief *et al.*[60] have developed equations for computing the maximal concentrations of nickel carbonyl that can be generated over

TABLE 4-13 Detection of Nickel Carbonyl in Air

Authors	Date	Method	Approximate Minimal Detectable Concentration in Air, ppb
Conlon and Taylor (personal communication)	1956	Nickel carbonyl reacts with bromine vapor to form nickel bromide, which is measured by light scattering	<100
McCarley *et al.*[384]	1956	Reflectance measurement	50
Kincaid *et al.*[304]	1956	Nickel carbonyl is trapped in solution of iodine in ethanol, and nickel is measured colorimetrically with dimethylglyoxime	2
Pitet[485]	1960	Nickel carbonyl reacts with sulfur dissolved in trifluoroethylene to form a precipitate, which is analyzed spectrographically	0.3
Ball *et al.*[24]	1960	Nickel carbonyl is detected by the effects of its pyrolysis products on gaseous conductance in an ionization chamber	5
Vol'berg[675]	1960	Nickel carbonyl reduces mercury oxide to mercury, and liberated mercury is measured by ultraviolet spectrometry	1
Belyakov[43]	1960	Nickel carbonyl is adsorbed with chloramine B in ethanol, and nickel is measured colorimetrically with dimethylglyoxime	10
Hunold and Pietrulla[263]	1961	Nickel carbonyl is trapped in solution of iodine in carbon tetrachloride, and nickel is measured colorimetrically with dimethylglyoxime	100
Densham *et al.*[120]	1963	Flame-emission spectrometry	40
		Ammonia-glyoxime colorimetry	6
		Atomic-absorption spectrometry	2
Brief *et al.*[60]	1965	Nickel carbonyl is trapped in dilute hydrochloric acid, and nickel is measured colorimetrically with α-furildioxime	0.8
Vol'berg and Gerskhovich[676]	1968	Nickel carbonyl reduces potassium iodate adsorbed on silica gel to liberate I^-, which is measured colorimetrically	0.1
Sunderman *et al.*[618]	1968	Nickel carbonyl is trapped in cold ethanol and measured by gas chromatography with electron-capture detection	<0.1
McDowell[387]	1971	Direct measurement of nickel carbonyl by infrared spectrophotometry	1

TABLE 4-14 Suggested Atmospheric Limits for Control of Exposure to Nickel Carbonyl[a]

	Concentration of Nickel Carbonyl in Air, ppb		
	Inside Industrial Plant		Outside Plant
Action	Single Air Sample	Daily Average	Monthly Average
Target values	40	1	0.3
Discontinue operation and require use of respirators	200–2,000	>1–5	–
Shut down operation	>2,000	>5	>1

[a] Derived from Stokinger.[572]

wide ranges of temperature, pressure, and carbon monoxide concentrations.

The importance of measurements of nickel in urine specimens from workmen who may be subject to accidental inhalation of nickel carbonyl has been emphasized.[192,205,304,417,555,584,593,680] Sunderman[584] reported 18,815 routine analyses of nickel in urine specimens from nickel carbonyl workers, which were performed during a 10-year period. Nickel concentrations were consistently below 6 μg/dl, except in cases of acute poisoning from nickel carbonyl. In Sunderman's experience,[584] measurements of nickel concentration in urine proved to be more practical than estimations of nickel excretion, because of the difficulty of obtaining carefully timed collections of urine from industrial workers. Nickel concentration in urine from healthy subjects was discussed in Chapter 3 (see Table 3-4); nickel concentration in urine from men who suffer acute nickel carbonyl poisoning was discussed earlier in this chapter.

Administration of chelating agents is the cornerstone of therapy for acute nickel carbonyl poisoning in man. As will be discussed below, on the basis of reported clinical experience, sodium diethyldithiocarbamate (dithiocarb) is currently the drug of choice for the treatment of nickel carbonyl poisoning. Although calcium–disodium ethylenediaminetetraacetic acid (edathamil) has been used, Morgan[417] observed little clinical evidence that administration of edathamil is therapeutically beneficial in nickel carbonyl poisoning. Indeed, animal experiments (West and Sunderman[706]) suggest that the administration of edathamil may actually be deleterious. Sunderman and Kincaid[588] reported that intramuscular administration of 2,3-dimercaptopropanol (dimercaprol, British antilewisite, BAL) to men with acute nickel carbonyl poisoning was attended by nickeluresis and by moderate clinical benefit. West and Sunderman[707] found that administration of β-dimethylcysteine (penicillamine) to mice afforded significant protection against acute nickel carbonyl poisoning. However, Lehnert and co-workers[334] reported that the administration of penicillamine to 15 healthy men caused prompt and significant diminution in the urinary excretion of nickel. There have not been any therapeutic trials of penicillamine in men who accidentally inhaled nickel carbonyl. In view of the observations of Lehnert *et al.*,[334] attempted penicillamine therapy for nickel carbonyl poisoning in man should be approached with caution.

Dithiocarb was first administered by Sunderman and Sunderman[594] to four workmen who had been severely exposed to inhaled nickel carbonyl. In these patients, the clinical manifestations of nickel carbonyl poisoning were relieved within a few hours after the initiation of oral therapy with dithiocarb, and the urinary excretion of nickel was promptly increased. With continued dithiocarb therapy, the patients made uneventful recoveries. Additional clinical experience with dithiocarb therapy for nickel carbonyl poisoning has been presented by Sunderman.[583,585] According to the most recent report,[585] 50 men with acute nickel carbonyl poisoning have been treated with dithiocarb. The initial urinary concentrations of nickel in these subjects ranged from 10 to 247 μg/dl. No deaths occurred among any of the patients who were treated with dithiocarb, and they were able to return to work within 3 weeks. In contrast, of 31 comparable patients with acute nickel carbonyl poisoning who were treated with dimercaprol,[587] two died. In the majority of the patients treated with dimercaprol, the period of convalescence lasted for several months.

Sunderman[585] has recommended the following therapeutic regimen for administration of dithiocarb in subjects who are known or thought to have been exposed acutely to hazardous atmospheric concentrations of nickel carbonyl:

> If there is any doubt regarding the extent or severity of exposure of a worker to nickel carbonyl an initial course of 2 g of Dithiocarb is given in divided doses. When 2 g of Dithiocarb are given in one dose, nausea usually develops. This may be lessened by administering the Dithiocarb in divided doses as follows: 0.2 g of Dithiocarb with water every 2 minutes for 10 doses along with 0.2 g sodium bicarbonate. If the symptoms of nickel carbonyl poisoning are minimal, decision regarding further therapy may be deferred until the results of the urine analysis for nickel are obtained.
>
> If the initial 8-hour specimen of urine has a nickel concentration of less than 10 μg per 100 ml, the exposure may be classified as *mild*. In such cases, it is probable that delayed symptoms will either not develop or will be minimal. Most patients in

> this group are able to continue work, although a few may complain of fatigue and require rest. If severe delayed symptoms develop unexpectedly, such patients are hospitalized and given Dithiocarb in a dosage schedule outlined for the *moderately severe* group.
>
> If the concentration of nickel in the first 8-hour collection of urine is above 10 μg but less than 50 μg per 100 ml, the exposure may be classified as *moderately severe*. Since delayed symptoms may develop in these patients, they should remain under careful observation for at least a week. Dithiocarb should be administered orally to these patients so that the total daily dosage on the first day of exposure amounts to 25 mg per pound of body weight (approximately 50 mg per kg). For a man weighing 160 pounds (80 kilograms), the daily dosage is, therefore, 4 grams. The suggested dosage schedule is:
>
> 2 grams (ten 0.2 g capsules)–0 hour
> 1 gram (five 0.2 g capsules)–4 hours
> 0.6 gram (three 0.2 g capsules)–8 hours
> 0.4 gram (two 0.2 g capsules)–16 hours
>
> On subsequent days Dithiocarb therapy should be continued in a dosage of 0.4 g every 8 hours until the patients are free of symptoms and the concentration of nickel in urine has decreased to the normal range.
>
> If the concentration of nickel in the first 8-hour collection of urine is above 50 μg per 100 ml, the exposure may be classified as *severe*. These patients are apt to be seriously ill and require hospitalization. Most of these patients can be maintained with oral Dithiocarb therapy as outlined for the moderately severe group. However, if the patient's condition is critical, it is suggested that Dithiocarb be administered *parenterally* in an initial dosage of 12.5 mg per pound of body weight (approximately 25 mg per kg). Additional doses should be given in accordance with the clinical evaluation. The total amount during the first twenty-four hours may be increased to as much as 50 mg per pound (100 mg per kg) of body weight.
>
> It is suggested that patients receiving Dithiocarb abstain from alcoholic beverages for one week following therapy. Patients receiving Dithiocarb who ingest alcoholic beverages may experience symptoms similar to those described after Antabuse.

There have been several recent investigations of similarities in the pharmacologic actions of dithiocarb and disulfiram (Antabuse). Dithiocarb and Antabuse are both potent inhibitors of aldehyde dehydrogenase activity in hepatic mitochondria. Dithiocarb is an intermediary metabolite of Antabuse.[144] It has been suggested[118] that dithiocarb may also undergo oxidation to Antabuse *in vivo*. Unlike Antabuse, dithiocarb has little inhibitory effect on drug metabolism by hepatic microsomes.[576] Antabuse and dithiocarb both inhibit hydroxylation of dopamine to norepinephrine by dopamine-β-oxidase.[93,344,695] Maj and Vetulani[355,356] and Maj *et al.*[354] reported that dithiocarb increased the concentration of dopamine and decreased the concentration of norepinephrine in rat brain and that it did not significantly affect the concentration of serotonin in rat brain. In view of the observed effects of dithiocarb on alcohol and catecholamine metabolism, physicians are advised to be very cautious regarding possible adverse drug interactions in patients who are receiving dithiocarb therapy for nickel carbonyl poisoning. Such sedatives as paraldehyde and chloral hydrate, tranquilizers, and other psychopharmacologic drugs are contraindicated. Pharmacologic investigations of the acute and chronic toxicity of dithiocarb have been reported.[76,464,590]

Administration of corticosteroids is probably a valuable adjunct to therapy for acute nickel carbonyl poisoning. Vuopala and co-workers[683] treated their patients who were hospitalized for nickel carbonyl poisoning with hydrocortisone (100–200 mg/day as an intravenous infusion) and prednisone (30–40 mg/day), with ampicillin as prophylaxis against infection. Digitalis and diuretics were also prescribed, according to the clinical situation. All their patients received oxygen by intranasal catheter, and one patient had to be placed in a Bennett respirator for 8 days after tracheostomy. All the patients in Vuopala's series survived.

5

Nickel and the Skin

PREVALENCE OF NICKEL DERMATITIS

It has been known for a long time that contact with nickel and with solutions of nickel salts may result in dermatitis. The problem of nickel contamination and associated skin contact in the United States is potentially serious, but no efforts have been made to define its magnitude. Systematic studies in the United States are few. Some investigators have reported a series of cases; many reports concern individual cases in which the vagaries of nickel dermatitis or new exposure factors are described. Many more cases undoubtedly have occurred and remained undocumented, but the exact number of cases in any year is unknown.

In the study by Baer *et al.*,[21] a comparison among selected patient populations of the incidence of allergic contact sensitivity to a group of common contact allergens between 1937 and 1961–1962 showed that the sensitivity to nickel had not changed significantly. In a recent study covering the period 1968–1970, Baer *et al.*[22] showed that the incidence of reactions to nickel sulfate has remained remarkably constant over approximately 35 years (12.3% in 1937, 11.2% in 1961, and 13.1% in 1968–1970). Nickel was ranked sixth in the group of the 24 most common contact allergens tested. However, the data do not seem sufficient to be statistically significant, in that only relative percentages are given, and not the numbers of cases. Surveys by European dermatologists for the decade of 1960–1970 are more informative and are summarized later.

Some studies in the American literature are pertinent. Gaul[187] reported that nickel produced the greatest number of cases and the most severe patch-test reactions in 68 cases of hand dermatitis. In a later study,[186] patch tests in 100 patients with various dermatoses showed 13 positive reactions to nickel. The sex ratio was impressive—12 women and one man. Fisher and Shapiro[162] found nickel to be the cause of dermatitis in 198 patients seen over a 5-year period at the New York Skin and Cancer Unit—180 women and 18 men from 16 to 63 years old. In Fisher's experience,[156] nickel caused more instances of contact dermatitis than all the other metals put together. He ranked nickel compounds (as a group) as having the third highest index of sensitization. In the extensive epidemiologic patch-test study carried out recently by members of the North American Contact Dermatitis Group,[146] nickel produced more positive reactions than any of the 15 other allergens tested. Thirteen dermatologists representing 10 centers participated in this study. Of the 1,200 subjects tested, 131 had positive nickel patch-test reactions (14 black females, 6 black males, 89 white females, and 22 white males), for an incidence of 11%. The percentage of nickel reactivity was almost twice that reported by the International Contact Dermatitis Research Group—6.7% in 4,825 patients (37 males and 284 females).[168]

European dermatologists have led in conducting epidemiologic studies. The importance allotted to nickel among the allergens varies from country to country. In France, it ranks seventh in importance.[327] Calnan's statistics of patients attending the patch-test clinic at St. John's Hospital for Diseases of the Skin (London) are significant.[73] Of 1,028 patients tested in 1953, 478 were positive reactors, and 131 were nickel-positive; of 891 patients tested in 1954, 412 were positive reactors, and 198 were nickel-positive; of 885 patients tested in 1955, 420 were positive reactors, and 180 were nickel-positive; and of 931 patients tested in 1956, 489 were positive reactors, and 146 were nickel-positive. Nickel was the commonest cause of allergic contact dermatitis in St. John's Hospital. Almost all those affected were women, and the exposure was mainly environmental. In the study by Marcussen,[371] the incidence of nickel allergy at the Finsen Institute (Copenhagen) was traced from 1940 to 1960. Analysis of representative years showed a rising curve—from 18 cases of nickel allergy per 1,000 cases of dermatitis in 1940 to 46 cases of nickel allergy per 1,000 cases of dermatitis in 1960. Environmental exposure was predominant (a result of wearing nickel on the skin); cases caused by occupational exposure showed only a slight increase. Rudzki and Kleniewska[502] investigated 1,205 patients in an epidemiologic study of contact dermatitis in Poland. They reported an incidence of 4.9% positive reactions to nickel—4.3% in men and 5.5% in women.

That nickel remains a common sensitizer was recently confirmed in two large groups of patients from Scandinavia and elsewhere in Europe who were patch-tested against a series of common allergens. In the Scandinavian series reported by Magnusson and co-workers,[353] six clinics in Norway, Denmark, Finland, and Sweden patch-tested 5,558 men and women. Of this group, 5.9% reacted positively to nickel. In the European study reported by Fregert and co-workers,[168] of 4,825 patients from Denmark, Sweden, Germany, The Netherlands, Italy, and England, 6.7% were reported as being sensitive to nickel on being patch-tested. Denmark and Sweden were represented in both investigations, but different patients were patch-tested in the two studies.

At the outpatient and inpatient clinic of the Nijmegen University (The Netherlands), Malten and Spruit[363] reported positive nickel patch tests in 4–9% of those suspected of suffering from contact dermatitis. In their series, 3,151 patients were tested in the 6-year period 1962–1967. Approximately two-thirds of the nickel patients were women. In a European series of 4,825 patients, Wilkinson and co-workers[713] assessed the role of contact dermatitis in hand eczema. They found that 11% of the women with hand eczema reacted positively to nickel; 9% of the women without hand eczema reacted positively to nickel. In another study of hand eczema, Agrup[5] patch-tested 712 persons—250 men and 462 women—with a standard test series; 56 (7.9%) reacted positively to nickel, and only women were affected. According to Cronin,[104] nickel remains the commonest sensitizer in women.

Although these findings are substantive, it should be noted that testing was limited to patients with eczema. The prime question of true incidence in the general population has not been answered, nor has the capacity of nickel to act as a skin sensitizer been fully evaluated.

From these data, it can be concluded that nickel allergy is an important problem in everyday life; in the general population, women have by far the higher incidence of contact allergy to nickel, and environmental exposure is responsible in a preponderance of cases.

ENVIRONMENTAL AND INDUSTRIAL SOURCES OF SKIN CONTACT WITH NICKEL

Occupational sources of exposure to nickel include nickel mining, extraction, and refining; plating, casting, grinding, and polishing; nickel powder metallurgy; nickel alloys and nickel–cadmium batteries; chemical industry; electronics and computers; food processing; and nickel waste disposal and recycling. Persons having possible skin contact with nickel occupationally, as listed by Adams[4] and Fisher,[156] include battery makers, nickel-catalyst makers, ceramics makers and workers, duplicating-machine workers, dyers, electronics workers, electroplaters, ink makers, jewelers, spark-plug makers, and rubber workers.

Nickel dermatitis is seen infrequently today as an occupational disease. Technologic improvements and advances in industrial medicine have helped considerably in controlling exposure in many industries. Marcussen,[370] in his review of the literature published between 1930 and 1960, noted that, although nickel dermatitis has largely disappeared in the major industries, more cases are being reported from minor occupations. For example, women are often exposed to nickel when working as salesgirls, cashiers, waitresses, and hairdressers.[327] In an investigation of cutaneous hazards in jewelry manufacturing[512] and ink making,[514] no cases of nickel dermatitis were observed. Nickel dermatitis remains a problem, however, in electroplating shops.[287]

Nonoccupational exposure to nickel is far more formidable, because the general population is affected. Sources of such environmental exposure include jewelry, coinage, clothing fasteners, tools, cooking utensils, stainless-steel kitchens, detergents, prostheses and other medical appliances, and tobacco smoke.

Malten and Spruit[363] reviewed the relative importance of various sources of environmental exposure to nickel in causing contact hypersensitivity. They attribute the primary localization and increased incidence of nickel dermatitis of the hands to the fact that there are two principal nonoccupational sources of contact with nickel: nickel commodities and nickel-containing detergents. In women, there are three main sources of rather continuous exposure to nickel during the day: jewelry, nickel-plated garment appliances, and stainless-steel kitchens.

The use of nickel commodities is increasing by 10% per year,[434] and the nickel-containing commodities that a person can contact are legion. Fisher[156] tabulated the nickel sources causing dermatitis as they affect different skin sites; such tables are helpful, but revisions are needed every few years because of the introduction of new products.

The role of detergent solutions containing nickel in the production of nickel dermatitis is controversial; it has been suggested by some investigators, but doubted by others. In a study by Wells,[705] the nickel content of detergents in England was less than 10 ppm; Malten and Spruit[363] found a nickel concentration of 2–9 ppm in commercial powders used in The Netherlands. These investigators concluded that such low concentrations of nickel are not likely to produce sensitization. To eliminate possible sensitization by nickel in detergents, EDTA was added to detergents in The Netherlands to chelate the nickel. The number of nickel-sensitive patients treated at the dermatology department of the Nijmegen University did not decline during the 3-year period after the addition of EDTA to detergent powders. (The inactivation of nickel with EDTA and other agents to prevent dermatitis is discussed at the end of this chapter.)

Malten and Spruit also implicated the American-style stainless-steel kitchen as a source of skin contact with nickel. Studies were not carried out to determine whether nickel is released from such stainless-steel commodities by reaction with sweat or sweat in combination with detergents, or whether enough nickel is released to provoke reactions if the contact is only ephemeral.

The potential of nickel in stainless steel to cause dermatitis must also be considered in the use of prostheses. Examples of nickel alloys implanted in man and animals are noted in Chapter 6. Tinckler[642] reported a case of skin sensitivity to surgical skin clips. An erythematous exudative eruption appeared on the eighth postoperative day, first at the site of a midline upper abdominal incision closed with metal skin clips and then spreading to involve a wider area of the abdominal wall, the elbow and knee flexures, and the buttocks. The eruption in all areas disappeared within 2 weeks of the removal of the metal skin clips. The patient's prior history revealed skin sensitivity to wristwatches, buckles, and collar studs. Patch tests with the surgical skin clips and nickel sulfide were positive (the clips were composed of cupronickel in the proportion of 80% copper to 10% nickel). A case of urticaria that occurred 2 months after fixation of a humeral fracture using Vitallium plate was reported by Symeonides *et al.*[626] The urticaria began to resolve 24 h after removal of the plate, and it had resolved completely by the third postoperative day. Reproduction of the same kind of skin reaction occurred after strapping of the Vitallium plate on the patient's arm; resolution of the urticaria occurred after removal of the strapped plate. Patch and scratch tests with nickel solution were positive (nickel is one of the Vitallium alloy components). Patch and scratch tests with the other components of the Vitallium plate were negative. Barranco and Soloman[29] reported a case of eczematous dermatitis from internal exposure to nickel from a stainless-steel screw in the patella. (Nickel sensitivity was demonstrated by patch testing: pure nickel, 3% nickel sulfate, and pieces of the stainless-steel screw yielded positive results; tests with metallic salts—such as potassium dichromate, cobalt sulfate, and mercuric chloride—were negative.) The stainless steel contained 14% nickel. The dermatitis subsided within 72 h after removal of the screw. This implies that nickel released from the stainless-steel screw produced the allergic reaction—a tenable thesis, inasmuch as Ferguson and co-workers[151] and Mears[395] have reported increased nickel concentrations in parenchymal tissues from implantation of stainless-steel rods containing nickel. Fisher, however, rejected the possibility of such reactions, on the grounds that the nickel is so firmly bound physically in the alloy that body fluids and perspiration cannot "leach" out the nickel to make it available to produce an allergic reaction.[159] He relies on the dimethylglyoxime test to prove the presence or absence of "available" nickel. Dimethylglyoxime produces a red precipitate on metallic objects or skin, if available nickel is present up to a dilution of 1:100,000.[513] To clarify the problem, Samitz and Klein[511] suggested the use of the dimethylglyoxime test on nickel prostheses in implanted areas and studies to determine whether changes in internal nickel concentrations caused by corroded nickel prostheses can provoke a reaction in a nickel-sensitive person.

LEACHING EFFECT OF SWEAT AND SOAPS TO RELEASE NICKEL AND FAVOR SKIN CONTACT

Samitz and Pomerantz[513] demonstrated the leaching of nickel from American coins through the action of human sweat or human sweat in combination with sodium lauryl sulfate. On the basis of these experiments and their experiments comparing patch tests made with quantitative dilutions of nickel sulfate prepared with water and with sodium lauryl sulfate solution, they proposed that sweat and detergents improve contact with skin and increase permeability. Inasmuch as sweat and detergent exposures in association with nickel are common both in industry and in the home, these findings may explain the frequency and ease of sensitization by nickel.

Such factors as sweat, friction, and penetration determine whether sensitive skin will react to the nickel content of a metal. According to Fisher,[156] sweating has a profound effect on the degree of dermatitis in nickel-sensitive persons, and dermatitis due to the nickel content of nickel-plated objects requires sweat for its development.

CLINICAL PATTERN OF NICKEL DERMATITIS

The early cases of nickel dermatitis in nickel miners, smelters, and refiners and nickel-plating workers were described as "nickel itch." The eruption began as an itching or burning papular erythema in the web of the fingers and spread to the fingers themselves, the wrists, and the forearms. With changes in environmental exposure, new clinical findings became manifest. Nickel dermatitis usually presents as a papular or papulovesicular dermatitis with a tendency for lichenification. The eruption usually has the characteristics of atopic dermatitis, rather than eczematous contact dermatitis. Another peculiarity of nickel dermatitis is its topographic distribution. In 1956, Calnan,[72] in an analysis of 400 cases, classified patterns of nickel dermatitis into three groups:

Primary. Areas in direct contact with metal.

Secondary. Selective symmetric areas involved when the dermatitis spreads (this occurs at some time in 75% of cases).

Associated. Areas of dermatitis that appear to have no relation to nickel sensitivity.

The primary pattern is self-explanatory: Any area of the skin may become affected if it is in contact with nickel. The secondary and so-called associated patterns are intriguing. According to Calnan, the secondary eruption did not occur in the nickel dermatitis encountered in workers in industrial exposure; nor does it conform to any special type of spread seen in any other types of contact dermatitis. There is no adequate explanation of this phenomenon. Theories involving such concepts as "metastatic eczema"[29] and "id eruption"[73] have been proposed. Fisher,[156] however, suggests that a careful history and close observation will reveal the "wandering" effect that nickel contact has over wide areas of the skin. Another puzzling feature of nickel dermatitis is that some cases persist for months after removal of the patient from evident sources of exposure (Samitz, unpublished data). Samitz postulates that the factors responsible for chronicity could result from fixation of nickel in the skin, subtle re-exposure to environmental nickel products, or an atopy–nickel relation (personal communication).

The pattern of nickel dermatitis is a sign of our times. Originally an occupational disease, nickel reactions appear today with much greater frequency in the general population, especially among women. In 1957, Calnan's series showed that 95% of affected women had suspender dermatitis as the first manifestation of nickel sensitivity.[71] Since the advent of panty hose, with which garter clips are not used, the incidence of garter-belt or suspender dermatitis has markedly decreased. The principal cause of nickel dermatitis now is probably costume jewelry, with earrings being the most frequent nickel sensitizer.[104]

RELATION BETWEEN NICKEL DERMATITIS AND ATOPIC DERMATITIS

The relation between nickel dermatitis and atopic dermatitis is not clear. Steiner[562] probably was the first to call attention to it; in his series, 9 of 16 patients with atopic dermatitis were allergic to nickel on being patch-tested. Epstein[147] reported that 10 of 34 patients with nickel sensitivity showed signs of atopic dermatitis as well. Dobson,[124] in discussing experimental nickel contact dermatitis, stated that nickel dermatitis is seen almost exclusively in atopic persons. The most distinct correlation was reported by Watt and Baumann:[690] Atopy was present as judged by heredity, case histories, and intracutaneous tests in 15 of 17 young girls with nickel dermatitis affecting the earlobes. Wilson,[717] Marcussen,[375] Caron,[78] Calnan,[72] and Fisher,[156] each in an independent study, found no significant connection between the two skin diseases. More recently, Wahlberg and Skog[686] measured immunoglobulin E (IgE) concentrations in 47 patients with nickel contact dermatitis (with a history of nickel exposure and positive patch tests with nickel) who had family and personal histories of atopy. Previous investigations by Juhlin *et al.*[285] and Johansson and Juhlin[281] had found IgE to be increased in patients with atopy. In only four of the 47 patients studied by Wahlberg and Skog was IgE content increased.

The occurrence of pustular patch-test reactions to nickel sulfate has also been considered as significant in the nickel–atopy relation. Fisher *et al.*[161] have emphasized that these reactions are not evidence of allergic sensitivity and that they occur frequently but not exclusively in persons with atopy. In Wahlberg and Skog's series, three of the patients had pustular reactions to 5% nickel sulfate solutions, but characteristic allergic reactions to lower concentrations.[686]

NICKEL SENSITIZATION

Experimental sensitization to nickel in guinea pigs has been reported by some investigators,[443,568,687] but their results have not been confirmed by others.[265,273,513] Nilzen and Wikström[443] reported a method for sensitizing laboratory animals to nickel by repeated topical applications of aqueous nickel sulfate solutions containing sodium lauryl sulfate. Samitz and Pomerantz[513] were unable to demonstrate sensitization with this technique; their results showed that sodium lauryl sulfate in combination with nickel sulfate produced a local irritation, rather than allergic reactions. Jansen *et al.*[275] suggested the possibility of inducing sensitization with nickel–alanine conjugate. Attempts to sensitize guinea pigs to nickel with an experimental chrome model[211] were unsuccessful. A technique for the consistent induction of delayed hypersensitivity to nickel in guinea pigs has not yet been developed.

Induction of sensitization with 25% nickel sulfate in man was reported by Haxthausen[227] and Burckhardt.[66] These investigators failed to test their subjects for prior sensitivity, and the 10% nickel sulfate used in challenge tests was sufficient to cause irritant responses. Vandenberg and Epstein,[668] using a "triple-freeze" technique, successfully sensitized 16 (9%) of 172 male subjects. Nineteen negative reactors previously exposed to nickel by the triple-freeze technique were re-exposed 4 months later by the same method. The results of the second triple freeze showed success in five subjects (26%). Hypersensitivity persisted; patch test 6 months later still produced strongly positive reactions.

Mechanism of Sensitization

It has been reasonably well established that, for simple chemicals to elicit epidermal sensitivity, it is necessary that the eliciting compound be applied to the surface of the skin, penetrate the epidermis, and combine with a body protein. The body reacts to this conjugated protein. In all likelihood, the specificity of the reaction is determined primarily by the haptenic portion of the molecule, the simple chemical; however, the carrier protein necessary to make the complex antigen need not be inert and may be the immunologic determinant. As part of a study of these underlying reactions, the mechanism of nickel sensitization requires elucidation in three categories of basic investigation:

Studies on the diffusion of nickel ions through the skin.

Studies on the chemical reactions of nickel ions with components of skin and soluble proteins.

Studies on the immunologic properties of antigens prepared *in vitro*.

DIFFUSION

Wells[705] showed that Ni^{2+} penetrates at sweat-duct and hair-follicle ostia and has a special affinity for keratin. Kolpakov[315] used cadaver skin as an experimental model to study the permeability of nickel compounds. The skin's barrier to the penetration of nickel sulfate was the stratum corneum. The malpighian layer of the epidermis, the dermis, and the hypodermis were readily permeable by nickel sulfate; the greatest accumulation of nickel was found in the malpighian layer, the sweat glands, and the walls of the blood vessels. When nickel sulfate was applied to the skin from the hypodermal side, it was adsorbed by the stratum lucidum, but it was not clear whether it could penetrate this layer. In another study of the effect of some organic solvents on the percutaneous absorption of nickel sulfate, Kolpakov showed by histochemical methods that the penetration of the epidermal barrier by nickel depended on the degree of the destructive effect of the organic solvent, as well as on the thickness of the stratum corneum.[314] In the study by Spruit *et al.*,[558] the changes of the potential of the dermis and the results of investigation of absorption and swelling all revealed that Ni^{2+} reaches and is bound to the dermis. Preliminary studies on the diffusion of nickel through skin using the chrome model (unpublished data) indicated that Ni^{2+} was less diffusible than Cr^{3+} and Cr^{6+}.

BINDING OF NICKEL

The binding of nickel to biologic substances (proteins, amino acids, peptides, ATP, nucleic acids, and porphyrins) is reviewed in Chapter 3. These data may be important in the elucidation of binding as it relates to nickel sensitization, and they can be extrapolated to experiments on the binding of nickel to skin constituents to determine antigenicity. Wells has shown that nickel has an affinity for keratin; on the basis of histochemical study, he thought it probable that the nickel was bound by the carboxyl groups of keratin.[705]

In 1964, Cotton[100] reported on the binding of nickel to several proteins. Using bovine serum albumin (BSA) as a model protein, he investigated the effects of denaturation and functional group modification on the binding of nickel and concluded that nickel was bound to both the amino and the carboxyl groups of the BSA. He also evaluated the reaction kinetics and the intrinsic stability constant of the nickel–BSA complex; he proposed that the complex was not sufficiently stable to warrant the consideration of nickel as a haptene capable of initiating an allergic response. The results reported by Magnus[352] support the idea of a low stability of the nickel–albumin complex. In his electrophoretic studies, he reported little tendency for the protein to bind nickel.

NICKEL COMPLEXES

The preparation and chemical properties of nickel–histidine complexes have been reported by Morris and Martin[419] and by Barns and Pettit.[25] Ferraro[153] reported a similar study on the nickel–alanine conjugate.

Jansen *et al.*[275] found that DL-nickel-alanine was a better sensitizer than the original allergen per molecule of applied substance. These data are pertinent to current studies in which complexes of nickel and amino acids found in the skin are being tested for antigenicity.

Techniques to Study Nickel Sensitivity

SKIN TESTING

The diagnosis of allergic contact dermatitis due to nickel is based on the history, character, and distribution of the eruption and on skin testing. The patch test is the classic method of establishing the cause of allergic contact dermatitis. It is a specific procedure that reproduces the patient's clinical disease in miniature.

Epstein[147] introduced the use of intradermal tests in cases of contact dermatitis from nickel and chromates. He considered the intradermal test as a phenomenon of practical as well as theoretical importance, because it could reveal cases of nickel contact allergy that yield negative patch tests. Routine use of this procedure was not recommended, because sensitization could be provoked. Marcussen[371] confirmed Epstein's work: A dilution of 1:10,000 nickel sulfate yielded a positive reaction in clinical nickel allergy and no reaction in controls. In another report,[369] Marcussen compared 5% nickel sulfate (for patch testing) and 1:10,000 nickel sulfate (for intradermal testing) in a series of 1,206 consecutive patients with dermatitis. Of this group, 62 had a positive intradermal test, whereas only 59 of them had positive patch tests. Two of the three patients with negative patch tests were retested later, and both reacted positively. In a study of 50 patients with nickel dermatitis, Fisher[156] found that 49 had positive intradermal tests; all 50 patients had positive patch tests. In no instance was the intradermal test with nickel superior to the patch test. Gottmann-Lückerath and co-workers[206] feel that intracutaneous tests should not be conducted routinely, but only to supplement routine patch testing—for detecting allergies to metals in persons with a positive history but negative patch tests and for distinguishing specific from nonspecific patch tests. From these studies, it can be concluded that patch tests and intradermal tests conform closely. Because patch testing is safe, easy to apply, relatively easy to interpret, and fairly specific, it remains the most important test to corroborate the diagnosis of nickel contact allergy.

Patch testing with nickel has some drawbacks:

1. The concentration of the testing solution is important. Using nickel

chloride as the testing agent, Vandenberg and Epstein[668] reported that 10% nickel chloride with occlusion caused too much irritation to be valuable in a predictive patch test. These investigators adopted a 5% nickel chloride patch covered (but not occluded) by a Band-Aid as the standard for their sensitizing experiments. Marcussen[374] reported on the specificity of patch tests with 5% nickel sulfate. However, he later reported that nickel sulfate in dilutions that were not irritating to the adult resulted in a high percentage of primary irritant reactions in children.[373] Recently, the North American Contact Dermatitis Group was formed to standardize patch-test technique and to develop a cooperative study on patch testing. A 2.5% nickel sulfate solution has been recommended. If nickel chloride is used for patch testing, they suggest that the solution be made up in an equivalent molar concentration.

2. Pustular patch-test reactions to nickel sulfate occur frequently and can confuse the physician. Such reactions represent a form of primary irritancy and cannot be interpreted as evidence of allergic sensitivity. Stone and Johnson[573] regularly produced pustular patch tests with 5% nickel sulfate over areas of induced inflammation. In the study by Fisher *et al.*,[161] 10% nickel sulfate produced the largest number of allergic eczematous reactions (5%) in 687 patients tested; only 1.3% had pustular reactions. These investigators reported that such reactions occur in only a minority of people and are not regularly reproducible. The pustules are asymptomatic and sterile and heal without clinical scarring. The reactions occur in persons with and without atopy.

OTHER TECHNIQUES

Lymphocyte transformation may be a sensitive *in vitro* technique for the detection of delayed hypersensitivity, compared with skin tests. Several recent contradictory studies have been reported concerning lymphocyte transformation by nickel ions. Aspegren and Rorsman[18] failed to demonstrate specific nickel stimulation of cultured lymphocytes in nickel-hypersensitive donors. Grosfeld *et al.*[209] found that when peripheral lymphocytes of nickel-sensitive subjects were cultured with nickel, there was no definitive difference in stimulation, compared with lymphocytes cultured without antigen. Pappas *et al.*[460] reported a nonspecific effect of nickel acetate on lymphocytes from patients with and without nickel sensitivity. In the study of MacLeod *et al.*,[350] when lymphocytes of 12 patients known (by patch testing) to be sensitive to nickel were stimulated in culture with nickel at 10^{-4} mEq/ml, the lymphocytes of only seven significantly took up [^{14}C]thymidine. This suggested that lymphocyte transformation was nonspecific and probably not as sensitive as patch testing or intradermal testing in determining nickel allergy. In a later study, however, the investigators definitively demonstrated the specificity of lymphocyte transformation *in vitro* by nickel salts in nickel-sensitive patients.[267] Lymphocyte-transformation tests were carried out in eight subjects with clinical and patch-test evidence of delayed hypersensitivity to nickel and in seven control subjects. Nickel sulfate and nickel acetate were used as antigens in the optimal nickel concentration of 10^{-4} mEq/ml. The findings indicated that increased lymphocyte transformation, as evidenced by increased thymidine uptake, occurred specifically in cells from nickel-sensitive subjects and that neither salt acted in a nonspecific stimulating capacity. These findings were confirmed by Forman and Alexander:[163] The lymphocyte-transformation test, estimated morphologically and by uptake of $[^{14}C]$thymidine, yielded evidence that, in nickel-sensitive persons, the lymphocytes were sensitized and reacted when challenged with 2.5% nickel sulfate. Milliken *et al.*[408] confirmed the specificity of the lymphocyte response to nickel ions in eight patients: The lymphocyte-transformation test correlated with patch-testing results for nickel sensitivity when optimal concentrations were used.

EFFECT OF NICKEL ON SKIN ENZYMES

The effect of nickel on enzymatic activity has been extensively reported in the literature and is reviewed in Chapter 3. A search of the literature for comparable experiments related to the effects of nickel on specific enzyme systems in the skin has not been rewarding.

ANALYSIS OF TRACE NICKEL IN HUMAN SKIN, HAIR, AND NAILS

Trace nickel in human skin, hair, and nails has not been extensively studied. Yurachek and co-workers[723] detected nickel in two hair samples studied by spark-source mass spectrometry. In one hair sample, the nickel concentration was 0.45 μg/g; in the other, 3.4 μg/g. Using the same analytic procedure, Harrison and Clemena[224] studied trace nickel in fingernails. Data from 17 subjects showed wide variation in concentration. Schroeder and Nason[531] and Nechay and Sunderman[431] have used atomic-absorption spectrophotometry to analyze trace metals in hair, as described in Chapter 3.

RELATION BETWEEN BIOLOGIC RESPONSES AND ABSORPTION OF NICKEL THROUGH SKIN

In a case reported by Sunderman and Sunderman,[592] a patient developed dermatitis of the hands, asthma, and Löffler's syndrome owing to the inhalation of nickel carbonyl. McConnell *et al.*[385] reported a case of contact dermatitis that preceded the manifestation of asthma associated with the inhalation of nickel salts. Both immediate and delayed hypersensitivity were demonstrated by scratch and patch tests. Stoddart[570] reported skin reactions (urticaria and pruritus in one instance and a generalized erythematous rash in another) in two patients with a history of nickel dermatitis who had had infusions. It was suggested that the cause was sensitivity to the nickel in the infusion cannulas.

Fidarov[154] studied the serum content of nickel and cobalt in patients with psoriasis. He reported slight increases in serum nickel and noted that, on improvement of the psoriasis, the nickel content decreased and approached normal.

RELATION BETWEEN NICKEL, COBALT, AND CHROMIUM IN SKIN SENSITIZATION

Hypersensitivity to groups of metals is the subject of controversy. Cross sensitivities among nickel, chromium, and cobalt were suggested by Marcussen.[371] Rostenberg and Perkins[499] proposed that there is a definite cross reactivity between nickel and cobalt, although they raise many questions concerning this immunologic phenomenon. However, in Fisher's experience, nickel does not react with other metals.[156] In commercial "nickel," cobalt is for all practical purposes inseparable,[368,499] and patch testing for possible nickel and/or cobalt dermatitis is confusing, because it is difficult to obtain nickel-free cobalt and cobalt-free nickel.[432]

Patients with allergic eczematous contact dermatitis due to metals are often allergic to more than one metal. Fregert and Rorsman[169] recently compiled a series of 5,416 patients who were suspected of having contact dermatitis. These patients were tested (patch and intracutaneous tests) with nickel, cobalt, and chromium. Of this group, 538 were found to react to one or more of the three metals; in 115 of the 538, there was allergy to both nickel and cobalt. In a review of 4,316 cases reported in the literature, da Fonseca[110] did not think it possible that there was hypersensitivity to groups of these metals by concomitant sensitization to various products at the same time or at different times. Pirila and

Kajanne[484] demonstrated that cement eczema can be caused by either cobalt or nickel and that combined sensitivity can be explained by regular mutual contamination of nickel and cobalt or their compounds. Others[372,574,662] have tried to approach the problem on the basis of the positions of metals in the periodic table.

PREVENTION OF NICKEL DERMATITIS

Once the diagnosis of nickel contact dermatitis is established, attention should be directed to the prevention of future attacks. It is easy to say that this could be readily accomplished by having the patient avoid contact with nickel, but the ubiquity of nickel in our environment makes this very difficult. Some guidelines for the patient are necessary, and various protective measures can be helpful.

The patient should be made aware of the nature of this problem. A list of nickel-containing items should be made available to him. Wherever possible, cloth or plastic substitutes should replace nickel-plated fasteners or other such appliances used in wearing apparel. Because most of the dermatitis occurs in areas of the skin in which there is close apposition of the metal and because sweat favors leaching of the metal, some protection can be afforded by decreasing the interface between skin and metal by applying talcum powder to lessen sweating and by introducing a physical barrier. To this end, some degree of protection has been afforded by the use of fingernail polish or lacquer[158] or a polyurethane coating.[420] Steroid aerosol spray has also been advocated.[160]

Research has been carried out with nickel-inactivating agents. Kurtin and Orentreich[318] reported the skin-blocking effect of calcium–disodium EDTA against nickel in nickel-sensitive patients. Samitz and Pomerantz[513] reported on the efficacy of 10% EDTA, 10% sodium diethyldithiocarbamate, and 10% dimethylglyoxime in polyethylene glycol ointment to inactivate patch-test reactions in nickel-sensitive patients. At present, no effective vehicle for these agents is available for use by the general population.

Teas and Milner described the use of multiple graduated doses of intradermal injections for hyposensitization in a patient with nickel dermatitis;[635] others have reported failures with this procedure.[638] Oral desensitization has also been tried, but without success.[157]

6

Nickel Carcinogenesis

EPIDEMIOLOGIC EVIDENCE OF NICKEL CARCINOGENESIS IN MAN

The epidemiologic studies of respiratory cancer that have been conducted among nickel refinery workers in Wales, Canada, Norway, and Russia have been thorough and carefully controlled. The epidemiologic data gathered in those countries will be discussed in detail here. The data available from Japan, Germany, and other countries are fragmentary and will be only briefly summarized.

Cancer in Welsh Nickel Workers

In 1932, a question was raised in England's House of Commons regarding an apparent propensity of workers at the Mond Nickel Works in Clydach, Wales, for cancer of the nasal cavities.[75,208] This nickel refinery, which used the nickel carbonyl process, had been in operation since 1900. Bridge[59] reported in 1933 that 10 cases (nine fatal) of cancer of the nasal cavities and paranasal sinuses had developed during the period 1921-1932 among workers at the refinery. By 1937, Baader[19] reported that 17 cases of cancer of the nasal cavities and 19 cases of pulmonary cancer were known to have occurred at the refinery.

Baader noted that the nasal cancer usually originated in the ethmoid sinuses. Sometimes, a necrotic polyp was present within the nose. The nasal cancer tended to penetrate the nasal bone and to enter the frontal sinuses or the orbit. Of 16 cases for which histologic specimens were available, three were epidermoid carcinomas and 13 were pleomorphic carcinomas. In 1949, Barnett[27] reported that 47 cases of cancer of the nasal cavities and 82 cases of cancer of the lung had been recognized in workers at the Welsh refinery in 1923–1948. Forty-six of the victims of cancer of the nasal cavities had died, and 72 of the victims of pulmonary cancer had died. Barnett stated that analysis of the cases up to the end of 1946 had shown that none of the workers with cancer of the nasal cavities and only two of the workers with pulmonary cancer had begun their employment in the nickel refinery later than 1924. In 1949, the Ministry of Pensions and National Insurance in Great Britain designated cancer of the nasal cavities and cancer of the lung as industrial diseases among some classes of nickel refinery workers, "in any occupation at a factory in which nickel is produced by decomposition of a gaseous nickel compound involving work in or about a building or buildings in which that process or an industrial process ancillary or incidental thereto is carried on."

The raw material used by the Mond Nickel Works consisted of a Bessemer matte that had been smelted in Canada and shipped to Clydach. The Bessemer matte contained approximately 46% nickel, 35% copper, 17% sulfur, and 0.8% iron. The matte was not radioactive. In Clydach, the matte was crushed, ground, and calcined to produce nickel and copper oxides. Most of the copper was leached out with sulfuric acid, and the residual nickel oxide was reduced to an impure nickel powder. The reduced nickel powder was vaporized as nickel carbonyl, and the nickel carbonyl was later decomposed to yield pure metallic nickel.

Although the basic industrial process has not been altered since 1900, there were progressive changes in the raw materials and in the design of the industrial facilities. These changes undoubtedly affected the composition of the dusts and fumes and greatly dimished the atmospheric concentrations of nickel and other substances to which the refinery workers were exposed. For example, from 1900 to 1921, arsenic was present as a contaminant in the sulfuric acid used to extract copper, whereas after 1921, the sulfuric acid was practically free of arsenic. Similarly, from 1900 to 1944, the Bessemer matte imported from Canada was rich in sulfur, whereas after 1944, the sulfur content of the matte was reduced to approximately 0.5%. To suppress the escape of dusts and fumes, improved calciners and automatic conveyors were installed in 1924; a centralized grinding plant was constructed in 1935; electrostatic precipitators were installed in the stacks in 1935; and new feed elevators and transporting devices were introduced in 1937.

Morgan[418] published a chronology of the nickel-refining processes at the Mond Nickel Works, with a detailed study of the occupational histories of nickel workers who were known to have developed cancer of the lung or nasal cavities. Morgan's observations indicated that the average interval between first employment in the nickel refinery and detection of pulmonary cancer was 27 years, compared with 23 years for cancer of the nasal cavities. There was wide variability in the interval between first employment and tumor detection. Thus, in 121 patients with lung cancer, the interval between first employment in the nickel refinery and occurrence of cancer ranged from less than 5 years to more than 40 years. Similarly, in 61 patients with nasal-cavity cancer, the interval ranged from less than 10 years to more than 40 years. Morgan demonstrated that the modifications of the refining processes were attended by a dramatic reduction in the incidence of respiratory cancer among nickel workers who began their employment at the refinery after 1924. Morgan suspected that arsenic in heated calcined dusts might have been partially or wholly responsible for the increased prevalence of respiratory cancer among the nickel workers who were employed before 1924.

There have been three major epidemiologic studies of respiratory cancer in Welsh nickel workers. The first was performed by Hill in 1939[243,244] and covered the years 1929–1935. Hill gathered data for the numbers and age distribution of men employed by the Mond Nickel Company or on the company's books as pensioners to estimate the population at risk for the period 1929–1938. As shown in Table 6-1,

TABLE 6-1 Mortality in Nickel Refinery Workers in Clydach, Wales, 1929-1938[a]

Cause of Death	No. Deaths: Observed	No. Deaths: Expected	Ratio of Observed to Expected
Cancer of lung	16	1	16 : 1
Cancer of nasal cavities	11	<1	>11 : 1
Cancer (all sites)	38	12	3.2 : 1
Cancer (excluding nasal cavities and lung)	11	10-11	1.0 : 1-1.1 : 1
All causes	105	84	1.3 : 1
All causes (excluding cancer)	67	72	0.9 : 1

[a] Derived from Hill.[243,244]

16 deaths from cancer of the lung and 11 deaths from cancer of the nasal cavities had been found in the Welsh nickel workers during the period. On the basis of the age-specific male death rates for England and Wales at that time, Hill estimated that one would have expected one death from cancer of the lung and a fraction of one death from cancer of the nasal cavities. In all other body sites, cancer was reported on the death certificates 11 times, and one would have expected 10–11 cases. There were 67 deaths from all other causes, whereas 72 deaths from all other causes would have been expected on the basis of the national death rates. Hill divided the nickel workers into two categories: "process workers," who had been directly concerned with the nickel refining processes; and "non-process workers," who had not been directly concerned with the refining processes. As shown in Table 6-2, all the excess deaths from respiratory cancer occurred in the process workers, although they constituted only 53% of the total number of employees.

The second epidemiologic study of the Welsh nickel workers was reported by Doll[125-127] in 1957 and 1958 and covered the years 1938–1956, considered in two separate periods, 1938–1947 and 1948–1956. Doll traced the death certificates of nearly all workers who had died during employment at the Mond Nickel Works and of a large proportion of pensioned workers whose last employment had been at the nickel refinery. These data were compared with data for men in two districts in South Wales (1938–1947) and in four districts (1948–1956) subdivided by the nature of last employment (Tables 6-3 and 6-4). Dur-

TABLE 6-2 Mortality in Nickel Refinery Workers in Clydach, Wales, June 1929–January 1938[a]

	No. Observed Deaths	
Cause of Death	"Process Workers"	"Non-Process Workers"
Cancer of lung	15	1
Cancer of nasal cavities	11	0
Cancer of other sites	7	5
Cancer (all sites)	33	6
Respiratory causes	13	10
Heart disease and cerebral hemorrhage	15	17
Other causes	7	7
TOTAL (all causes)	68	40[b]

[a] Derived from Hill.[243,244]

[b] Includes three deaths among office staff not included in Table 6-1.

TABLE 6-3 Mortality from Cancer of Lung and Nasal Cavities among Men Residing in Two Local Authority Areas of South Wales, 1938-1947[a]

Last Employment	Total No. Deaths	Deaths from Lung Cancer		Deaths from Nasal-Cavity Cancer	
		No.	%	No.	%
Nickel industry	144	36[b]	25.0	16[c]	11.1
Steel industry	827	22	2.7	1	0.1
Coal mining	1,080	8	0.7	1	0.1
Other selected occupations[d]	46	0	0.0	0	0.0
All other occupations	1,731	29	1.6	2	0.1
TOTAL	3,828	95	2.5	20	0.5

[a] Derived from Doll.[125-127]

[b] Expected deaths from experience of men in "all other occupations" = 2.61. Ratio of observed to expected = 13.8 : 1.

[c] Expected deaths from national mortality statistics = 0.066. Ratio of observed to expected = 242 : 1.

[d] Men employed in aluminum, copper, smelter, patent-fuel, and oil refineries and factories.

TABLE 6-4 Mortality from Cancer of Lung and Nasal Cavities among Men Residing in Four Local Authority Areas of South Wales, 1948–1956[a]

Last Employment	Total No. Deaths	Deaths from Lung Cancer		Deaths from Nasal-Cavity Cancer	
		No.	%	No.	%
Nickel industry	200	48[b]	24.0	13[c]	6.5
Steel industry	2,179	121	5.6	3	0.1
Coal mining	2,804	73	2.6	2	0.1
Other selected occupations[d]	661	54	8.2	1	0.2
All other occupations	9,403	503	5.3	6	0.1
TOTAL	15,247	799	5.2	25	0.2

[a] Derived from Doll.[125,127]

[b] Expected deaths from experience of men in "all other occupations" = 9.88. Ratio of observed to expected = 4.9 : 1.

[c] Expected deaths from national mortality statistics = 0.082. Ratio of observed to expected = 159 : 1.

[d] See Table 6-3.

ing the period 1938–1947, 36 of 144 deaths among the nickel workers were attributed to cancer of the lung (25%), and 16 were attributed to cancer of the nasal cavities (11%). The proportions of deaths from pulmonary and nasal-cavity cancer among steelworkers, colliery workers, and other occupational groups (Table 6-4) were close to those that would have been expected on the basis of the age-specific male mortality data for England and Wales. Doll estimated that during 1938–1947, the nickel workers' risk of dying from pulmonary cancer was 13.8 times the expected risk, and the risk of dying from cancer of the nasal cavities, 242 times the expected risk. During the period 1948–1956 (Table 6-4), 48 of 200 deaths among nickel workers were attributed to cancer of the lung (24%), and 13 were attributed to cancer of the nasal cavities (6.5%). Doll estimated that during 1948–1956, the nickel workers' risk of dying from pulmonary cancer was 4.9 times the expected risk, and the risk of dying from cancer of the nasal cavities, 159 times the expected risk. He found that the nickel workers were not all equally at risk of developing respiratory cancer. Of the 48 nickel workers whose deaths were attributed to pulmonary cancer during 1948–1956, 28 (58%) were described as having been employed directly in the nickel-refining processes ("process workers"). Doll estimated that the risk of lung cancer among the process workers was 7.1 times the expected risk. In comparison, the risk of lung cancer among nonprocess workers was 3.4 times the expected risk. Of the 29 nickel workers whose deaths were attributed to cancer of the nasal cavities during 1938–1956, 19 (66%) were process workers. Doll computed that the risk of cancer of the nasal cavities among the process workers was 247 times the expected risk. In comparison, the risk of cancer of the nasal cavities among the nonprocess workers was 119 times the expected risk.

The third epidemiologic study of Welsh nickel refinery workers was reported by Doll *et al.* in 1970.[128] They studied 845 men who had been employed at the nickel refinery for at least 5 years and whose first employment was before May 1944. All but 3.2% were traced until death or January 1967. All together, 482 of the men had died—113 (23%) from lung cancer and 39 (8%) from cancer of the nasal cavities. The number of deaths that would have been expected if those men had suffered the normal mortality experience in England and Wales was calculated by multiplying the man-years at risk in each calendar period by the corresponding annual age-specific male mortality rates for the entire nation. For cancer of the nasal cavities, age-specific rates were not available before 1950, and the rates for 1950–1954 were used for the earlier years. This assumption was justified by the fact that the crude mortality rate for cancer of the nasal cavities was approximately constant from the early 1940's on.

The distribution of deaths by cause and year of first employment is shown in Table 6-5. Men who started employment between 1900 and 1925, taken as a whole, suffered a mortality from cancer of the nasal cavities that averaged 364 times the national average. No deaths from this cancer occurred in men who started in 1925 or later. Men who started employment between 1900 and 1925, taken as a whole, suffered a mortality from pulmonary cancer that averaged 7.5 times the national average. The mortality rate from lung cancer in men who began employment in the refinery after 1925 was only 1.3 times the national average. The mortality from other cancers among men employed between 1900 and 1925, taken as a whole, was slightly increased (1.6 times the national rates, $p < 0.01$), but was not increased among men who were employed after 1925. Doll *et al.* speculated that much of the excess mortality from other cancers among men employed before 1925 was due to diagnostic confusion with cancer of the lung. Mortality from all other causes was approximately 1.2 times that predicted from the national statistics, regardless of when employment began. This corresponded to the excess mortality normally reported for the region of South Wales where the nickel refinery is.

The findings of Doll *et al.* confirmed the earlier reports[27,418] that the respiratory-cancer hazard in the Clydach nickel refinery had been elimi-

TABLE 6-5 Mortality in Nickel Refinery Workers in Clydach, Wales[a]

Cause of Death	Year of First Employment	No. Deaths		Ratio of Observed to Expected
		Observed	Expected	
Cancer of lung	1900–1915	49	4.86	10.1 : 1
	1915–1924	56	9.08	6.2 : 1
	1925–1944	8	6.06	1.3 : 1
Cancer of nasal cavities	1900–1915	28	0.049	571 : 1
	1915–1924	11	0.058	190 : 1
	1925–1944	0	0.036	–
Cancer of other sites	1900–1915	19	15.61	1.2 : 1
	1915–1924	30	15.89	1.9 : 1
	1925–1944	9	9.16	1.0 : 1
All other causes	1900–1915	97	91.84	1.1 : 1
	1915–1924	117	85.34	1.4 : 1
	1925–1944	58	48.49	1.2 : 1
All causes	1900–1915	193	112.37	1.7 : 1
	1915–1924	214	110.35	1.9 : 1
	1925–1944	75	63.74	1.2 : 1

[a] Derived from Doll.[128]

nated by the beginning of 1925. Several men who developed cancer of the nasal cavities were first employed in 1923 or 1924, and it seems likely that the crucial change in industrial exposure took place toward the end of 1924 or the beginning of 1925. Doll and co-workers[128] reported that susceptibility to induction of cancer of the nasal cavities increased with age at first exposure ($p < 0.05$), but that susceptibility to induction of pulmonary cancer was not similarly correlated. Doll *et al.* emphasized the need for study of the possible relation of cigarette smoking to the development of pulmonary cancer in nickel workers, and they stated that, unfortunately, they had not been able to obtain data on smoking habits.

On the basis of a personal communication from Dr. Lindsay G. Morgan, the status of respiratory-cancer statistics for the Clydach nickel refinery as of December 31, 1971, was as follows: Cancer of the nasal cavities had been recognized in 78 subjects, of whom one had entered employment in 1929. Pulmonary cancer had been recognized in 174 subjects, of whom 25 had entered employment after 1925. During the 10 years from 1961 to 1971, 14 new cases of lung cancer had been observed, whereas 11 cases of lung cancer would have been expected on the basis of national statistics. This increase was not statistically significant.

Cancer in Canadian Nickel Workers

Canada has large deposits of nickel ores that are particularly abundant in the Sudbury district of the Province of Ontario. The bulk of Canadian nickel ore is mined and smelted in the Sudbury region. Since 1900, matte containing nickel and copper sulfides has been shipped from Canada to Clydach, Wales, for refining by the nickel carbonyl process, as described earlier. Between 1918 and 1926, a new nickel refinery came into production at Port Colborne, near Niagara Falls on Lake Erie. At this refinery, the nickel–copper sulfide matte from Sudbury was calcined and roasted, and nickel was refined by the electrolytic process. Cancer of the nasal cavities and lung was first detected among workers at the Port Colborne nickel refinery in 1946.

An epidemiologic study of respiratory cancer at the Port Colborne refinery was conducted by Sutherland[624] in 1959, covering the period 1930–1957. Sutherland gathered data on all employees at the refinery with 5 years or more of service who were on the payroll in January 1930 or who later acquired this length of service. Among these 2,355 workmen, there were 245 deaths, including 19 from pulmonary cancer and seven from cancer of the nose and paranasal sinuses. Age-specific male death rates for Ontario were used to calculate the expected number of deaths in the population (Table 6-6). Sutherland estimated that during 1930–1957, the nickel workers' risk of dying from cancer of the nasal cavities was 37 times the expected risk, and the risk of dying from pulmonary cancer, 2.2 times the expected risk. A review of the experience of residents in the Port Colborne area during 1950–1957 did not show that any increased risks of cancer of the nose or lungs were associated with residence in the community.

During the period 1958–1967, 16 additional cases of cancer of the nasal cavities and 46 cases of cancer of the lung occurred among workmen at the Port Colborne refinery, yielding totals of 23 cases of cancer of the nasal cavities and 65 cases of pulmonary cancer.[380,672] To determine whether some workers faced particularly great risks of developing respiratory cancer, the nickel refinery workers who died from 1958 to 1965 were subdivided into eight exposed groups, as shown in Table 6-7. Furnace workers were found to have the greatest risk of mortality from cancer of the nasal cavities and lung. The data suggested that exposure for 6 months or more in cupola-furnace operations or exposure for 3 years or more in sintering-furnace operations was associated with increased risk of mortality from both nasal-cavity and pulmonary cancer. No increased risk of cancer of the lung or nasal cavities was associated with employment solely at calcining furnaces, solely at the anode furnace in the electrolytic plant, in nondusty exposures, or in office work. As a result of the investigations by Sutherland,[624] major changes were made in the nickel-refining processes to eliminate exposures that

TABLE 6-6 Mortality in Nickel Refinery Workers in Port Colborne, Ontario, 1930–1957[a]

Cause of Death	No. Deaths		Ratio of Observed to Expected
	Observed	Expected	
Cancer of lung	19	8.45	2.2 : 1
Cancer of nasal cavities	7	0.19	36.8 : 1
Cancer (all sites)	54	43.19	1.3 : 1
Cancer (excluding nasal cavities and lung)	28	34.55	0.8 : 1
Vascular disease (including central nervous system)	14	20.72	0.7 : 1
Respiratory disease	13	16.21	0.8 : 1
Gastrointestinal diseases	9	16.07	0.6 : 1
All causes	245	308	0.8 : 1

[a] Derived from Sutherland.[624]

TABLE 6-7 Mortality from Cancer of Lung and Nasal Cavities in Nickel Refinery Workers in Port Colborne, Ontario, 1930-1965[a]

Exposure Group	No. Deaths from Cancer of Lung			No. Deaths from Cancer of Nasal Cavities		
	Observed	Expected	Ratio of Observed to Expected	Observed	Expected	Ratio of Observed to Expected
(1) Furnace workers	8	1.88	4.3 : 1	5	0.023	21.7 : 1
(2) Other dust workers	4	1.89	2.1 : 1	0	0.029	–
(3) Electrolysis workers	1	1.26	0.8 : 1	0	0.014	–
(4) Nondust workers	0	1.07	–	0	0.011	–
(5) Office workers	2	0.41	4.9 : 1	0	0.006	–
(6) Mixed: < 3 years in (1) and (2) plus other work	6	2.57	2.3 : 1	2	0.035	57 : 1
(7) Mixed: ≥ 3 years in (1) plus other work	15	2.15	7.0 : 1	8	0.026	308 : 1
(8) Mixed: ≥ 3 years in (2) plus other work	1	1.47	0.7 : 1	1	0.022	45 : 1
TOTAL (all workers)	37	12.70	2.9 : 1	16	0.166	96 : 1

[a] Derived from Mastromatteo.[180]

were associated with increased risk of respiratory cancer. Cupola-furnace operations had already been eliminated in 1931, and sintering-furnace operations were terminated in 1962. Calcining operations were also curtailed.

In the 1960's, cancer of the respiratory tract began to be recognized among workers in the sintering plant at another nickel refinery, in Copper Cliff, near Sudbury, Ontario. The first death from lung cancer occurred in 1960, and two deaths from lung cancer and one from cancer of the nasal cavities occurred in 1966. In 1969, Sutherland[623] performed an epidemiologic study of mortality from respiratory cancer at this sintering plant, using essentially the same methodology as he had previously used in the study of the Port Colborne refinery. Sutherland obtained occupational histories of 525 men. Of these, 42 were excluded from the study, because they had worked in the sintering plant for less than 6 months. Of the remaining 483 men, 21 had died before July 1968, including seven (33%) from pulmonary cancer and one (5%) from cancer of the nasal cavities (Table 6-8). The cases of cancer of the lung and nasal cavities were all confirmed by histologic examination. The shortest interval between first exposure and development of lung cancer was 8.3 years, and the average interval was 15.5 years. The case of cancer of the nasal sinuses developed 17.3 years after first exposure to nickel refining. According to Sutherland (personal communication), there have been 20 additional cases of lung cancer among nickel workers at this sintering plant in Copper Cliff. It may be relevant that the sinter produced at this plant contains less than 1% sulfur. At the same smelter in Copper Cliff, during the years 1950–1967, there was no excess mor-

TABLE 6-8 Mortality in Nickel Sintering Plant Workers in Copper Cliff, Ontario, January 1948–June 1968[a]

	No. Deaths		
Cause of Death	Observed	Expected	Ratio of Observed to Expected
Cancer of lung	7	0.78	9.0 : 1[b]
Cancer (all other sites)	1	2.65	0.4 : 1
Vascular diseases	3	9.00	0.3 : 1[b]
Other diseases	4	3.69	1.1 : 1
All diseases	15	16.12	0.9 : 1
Accidents, poisoning, and violence	6	5.35	1.1 : 1
All causes	21	21.47	1.0 : 1

[a] Derived from Sutherland.[624]

[b] $p < 0.01$.

tality from respiratory cancer among workers in nickel-converter operations who were exposed to intermittent high concentrations of metallic dusts and sulfur dioxide. At two additional sintering plants in the Sudbury region, which are engaged in processing nickel sulfide ore, there have been no cases of cancer of the nasal cavities and only a few cases of lung cancer. At these two plants, sintering is performed at a lower temperature, and the product contains 18–22% sulfur. Some of the product from these plants is shipped to Norway for further refining.

Cancer in Norwegian Nickel Workers

A nickel-refining plant was constructed in Kristiansand, Norway, in 1910 to process nickel–copper matte from a smelter at Evje, Norway. The nickel refinery in Kristiansand was acquired by a Canadian company in 1928 and since then has refined nickel–copper sulfide matte, which has been shipped to Norway from Falconbridge, near Sudbury, Ontario. The matte contains approximately 48% nickel, 27% copper, and 22% sulfur. At the Kristiansand refinery, the matte is ground to pass through a 10-mesh screen and then is roasted in a multihearth roaster to remove sulfur. The roaster product is leached with sulfuric acid to extract copper and filtered to produce a nickel cake. The nickel cake is reduced with hydrogen to produce impure nickel. The residue of the leaching tank is dried and reduced to impure nickel in an electric furnace; coke is used as a reductant. The impure nickel is cast into anodes, which are refined electrolytically to produce pure nickel cathodes for market.

Between 1920 and 1971, the annual production of nickel at the Kristiansand refinery increased by a factor of 40. By far the largest absolute increase in number of tons produced per year has occurred since 1950. Production practically ceased during the war years, 1940–1945. The number of employees increased from about 250 in 1922 to around 500 by 1940; after 1945, there was a further increase, to approximately 1,500 by 1971. Cases of respiratory cancer among nickel workers in Kristiansand were first recognized by Løken[345] in 1950. Løken described squamous cell carcinomas of the lung in three men who had worked at the refinery for 10, 22, and 27 years. Two of the men had been furnace workers, and the third had for many years been shearing nickel. Between 1950 and 1955, Løken observed two additional cases of pulmonary cancer among workmen at the nickel refinery (cited in Goldblatt and Goldblatt.[203(p. 209)]

An epidemiologic study of respiratory cancer among the nickel refinery workers at Kristiansand, Norway, has been reported by Pedersen *et al.*[470] and covers the 19-year period, 1953–1971. Analysis was confined to men whose first employment at the refinery had started before 1961 and who had been employed for at least 3 years. A total of 1,916 workmen met these criteria. The definition of the follow-up period implied that men who had died before 1953 were excluded from the analysis. A man was considered "under observation" from the beginning of 1953 or, if he was first employed during the period 1953–1960, from the middle of the year in which his employment started. Each man was followed until death or to the end of 1971. Computations of expected deaths from cancer and other causes were based on the age-specific national mortality rates by 5-year age groups for each calendar year during 1953–1970. The results of the investigation of Pedersen *et al.*[470] are summarized in Table 6-9. During 1953–1970, there were 48 cases of lung cancer, 14 cases of cancer of the nasal cavities, and five cases of laryngeal cancer. The ratios of observed to expected numbers of cases of cancer of the lung and nasal cavities indicate that the highest risk was among men who started working in the plant from 1910 to 1929. The ratios were smaller for workers who started in successive periods thereafter.

The interpretation of this trend is not at all straightforward. The average interval between start of employment and manifestation of respiratory cancer was very long, and the downward trend of the ratios could to some extent be a reflection of this. A substantial part of the excess risk of those employed in the early years was due to the high incidence of cancer of nasal cavities among them. Of a total of 14 such cases, 13 were among men first employed before 1940. Pedersen *et al.*[470] emphasized that it was not justified to conclude from the data that the hazard of nasal-cavity cancer had been reduced after 1945, because the average interval between start of employment and manifestation of nasal-cavity cancer was 31.6 years in these cases and was less than 20 years in only one case. One man who started emplovment in 1948 developed cancer of the nasal cavity in 1970. Regarding lung cancer, it is clear that the hazard of exposure still persisted around 1950.

The highest risk of mortality from cancer of the respiratory tract was among men involved in roasting, smelting, and electrolysis (Table 6-10). For the 1,071 men who were included in groups 1 and 2 (roasting, smelting, and electrolysis), the ratios of observed to expected numbers of cases were 6.21:1 for lung cancer and 37:1 for cancer of the nasal cavities. Although the number of cases of laryngeal cancer was small, the fact that four of the five cases were in workers who were engaged in roasting and smelting is certainly remarkable. Pedersen *et al.*[470] com-

TABLE 6-9 Mortality from Cancer of Lung and Nasal Cavities in Nickel Refinery Workers in Kristiansand, Norway, 1953–1971[a]

Year of First Employment	No. Men	No. Deaths from Lung Cancer: Observed	Expected	Ratio of Observed to Expected	No. Deaths from Nasal-Cavity Cancer: Observed	Expected	Ratio of Observed to Expected
1910–1929	106	10	0.96	10.4 : 1	6	0.06	100 : 1
1930–1940	282	11	2.44	4.5 : 1	7	0.11	64 : 1
1945–1954	1,091	23	5.20	4.4 : 1	1	0.23	4.3 : 1
1955–1960	437	4	1.57	2.5 : 1	0	0.07	—
TOTAL	1,916	48	10.17	4.7 : 1	14	0.47	29 : 1

[a] Derived from Pedersen *et al.*

TABLE 6-10 Mortality from Cancer of Lung and Nasal Cavities in Nickel Refinery Workers in Kristiansand, Norway, 1953–1971[a]

Category of Work	No. Men	No. Deaths from All Causes			No. Deaths from Lung Cancer			No. Deaths from Nasal-Cavity Cancer		
		Observed	Expected	Ratio of Observed to Expected	Observed	Expected	Ratio of Observed to Expected	Observed	Expected	Ratio of Observed to Expected
(1) Roasting, smelting	462	95	75.7	1.3 : 1	12	2.5	4.8 : 1	5	0.1	50 : 1
(2) Electrolysis	609	139	108.5	1.3 : 1	26	3.6	7.2 : 1	6	0.2	30 : 1
(3) Other specified processes	299	37	39.8	0.9 : 1	6	1.3	4.6 : 1	1	0.1	10 : 1
(4) Other and unspecified work	546	74	79.7	0.9 : 1	4	2.7	1.5 : 1	2	0.1	20 : 1
TOTAL	1,916	345	303.7	1.1 : 1	48	10.1	4.8 : 1	14	0.5	28 : 1

[a] Derived from Pedersen *et al.*[illegible]

mented that the data did not permit any firm conclusion regarding an increased risk of laryngeal cancer among nickel workers, but they do suggest that this may be another manifestation of risk related to occupational exposure to nickel.

Cancer in Russian Nickel Workers

In 1963, Znamenskii[726] reported that many cases of cancer of the nasal cavities and several cases of cancer of the lung had occurred at various nickel refineries in the Soviet Union among workers engaged in extracting, isolating, and reprocessing nickel ore. Specific numbers of cases were not included in Znamenskii's brief account, nor was there discussion of the relative incidence of cancers of the respiratory tract among the workers. Tatarskaya[632,633] reported that, between 1959 and 1965, six cases of cancer of the nasal cavities and three cases of pulmonary cancer had occurred among workmen at two electrolytic nickel refineries. The refineries had apparently been in operation for 20–23 years, and the nickel workers had been exposed to aerosols of electrolyte that consisted of nickel sulfate, nickel chloride and very small amounts of cobalt, copper, and iron salts. There was no exposure to nickel carbonyl. There was no statement as to whether the workers had any exposure to furnace operations.

An epidemiologic investigation of cancer among Russian nickel workers reported by Saknyn and Shabynina[510] in 1972 covered the years 1955–1967. Cancer mortality among workers at a nickel refinery in the Urals was compared with the cancer mortality of the population of an adjoining city. The nickel ore was prepared by briquetting, and the refining processes included drying, smelting, roasting–reduction, and ancillary operations, including cobalt production. The nickel refinery converted oxidized ores that contained up to 1% nickel, 40–50% silicon dioxide, and unspecified amounts of iron and aluminum. No electrolysis was performed at the refinery. The workers were exposed primarily to inhalation of nickel sulfide and nickel oxide dusts, but cobalt and arsenic dusts were also present in the cobalt production facility. The results of the study are summarized in Table 6-11.

No data were given for the number of cases of cancer, nor for the population at risk. Saknyn and Shabynina stated that the highest cancer mortality among the workers was from pulmonary cancer. The pulmonary-cancer mortality among old workers at the nickel refinery was 1.8 times that among the population of the neighboring city. Among the nickel workers, pulmonary cancer was found only in men aged 40 and older. The workers who died of lung cancer had worked in the refinery for an average of 13 years. The industrial processes associated with the greatest risk of mortality from lung cancer included the roasting-reduction operation, in which workers were exposed to nickel sulfide and nickel oxide dusts, and the cobalt production facility, in which workers were exposed to nickel, cobalt, and arsenic dusts. There was no mention of any cancer of the nasal cavities among the workers. Saknyn and Shabynina observed a statistically significant but unspecified increase in mortality from gastric carcinoma among workers aged 50 and older. Mortality from sarcomas (femoral and pulmonary) among the nickel refinery workers was increased by a factor of 6.2, compared with that in the urban population. The deaths from sarcomas occurred primarily among men aged 40 and older. Saknyn and Shabynina recently reported a more comprehensive epidemiologic study of cancers among Russian nickel workers. They observed significantly increased frequencies of cancers of the lung and stomach and various sarcomas among workmen at four different nickel refineries. They suggested[509] that gastric cancer may warrant consideration as an occupational disease in the nickel industry.

Cancer in Nickel Workers in Other Countries

In 1965, Tsuchiya[656] examined the health records of the Japanese Ministry of Health to identify industries that were associated with excessive mortality from cancer of the lung and other organs. During the period 1957–1959, 494 cancer deaths were reported in Japan among 1,200,000 workers aged 20–59. The workers were employed in 200 major categories of industry. Tsuchiya observed a significant association between lung cancer and industrial exposure to nickel. During the 3-year period, 19 cases of lung cancer were reported among workmen who were exposed to nickel an incidence significantly greater than expected ($p < 0.01$). Tsuchiya's report did not provide any information concerning the types of industrial exposures to nickel that were associated with pulmonary cancer and did not mention cancer of the nasal cavities.

In 1958, Rockstroh[497] published a report on pulmonary cancer in nickel workers at a refinery in Aue in Saxony, Germany. The nickel-refining processes included smelting, roasting, crushing, production of nickel sulfate, and electrolysis. During 1932–1953, 45 cases of pulmonary cancer had been observed among the nickel production workers. The average number of nickel production workers was 111 during the period of observation. Rockstroh noted that only one case of pulmonary cancer had been found among other workers at the same plant

TABLE 6-11 Mortality Indexes for Cancer of All Sites in Nickel Refinery Workers in the Urals Region of Russia, 1955-1967[a]

Refinery Processes	Ratio of Observed to Expected No. of Cases of Cancer					
	Male Workers			Female Workers		
	40-49 yr old	≥ 50 yr old	All	40-49 yr old	> 50 yr old	All
Smelting	3.6 : 1	2.4 : 1	1.0 : 1	5.1 : 1	8.9 : 1	1.3 : 1
Roasting and reduction	3.8 : 1	6.6 : 1[b]	2.4 : 1[b]	5.4 : 1	3.5 : 1	1.2 : 1
Preparation and drying	4.9 : 1	2.[illegible] : 1	1.3 : 1	–	19.1 : 1[b]	1.3 : 1
Cobalt production	4.3 : 1	5.3 : 1	1.8 : 1[b]	–	2.6 : 1	0.4 : 1
All refining processes	4.0 : 1[b]	4.3 : 1[b]	1.5 : 1	2.7 : 1	7.3 : 1[b]	1.1 : 1
Entire industrial plant	3.2 : 1[b]	3.7 : 1[b]	1.5 : 1[b]	2.8 : 1[b]	5.0 : 1[b]	1.1 : 1

[a] Derived from Saknyn and Shabynina.[110]

[b] $p < 0.01$.

who were not involved in nickel production, and he concluded that there was probably a causal relation between exposure to nickel and the development of pulmonary cancer. However, Rockstroh emphasized that the nickel workers had generally worked in various departments of the plant and had also been exposed to arsenic, cobalt, pesticides, and other substances. He suggested that inhalation of combinations of nickel compounds and other toxic and irritant substances might be important in the pathogenesis of pulmonary cancer.

Two reports from France and one from the United States have described cancer of the respiratory tract in workers who were not employed in nickel refineries, but who were involved in nickel plating and grinding. Bourasset and Galland[54] reported a reticulosarcoma of the nasal fossa in a 59-year-old woman who had been engaged in electrolytic nickel plating in a cutlery factory. She had been chronically exposed to the inhalation of vapors containing nickel and ammoniacal products of electrolysis. The period between first exposure and appearance of the sarcoma was 5 years. Touraine and Rambaud[651] reported the simultaneous occurrence of two distinct primary epidermoid carcinomas in the left lung of a 53-year-old man who had been employed in an electrolytic plating shop. In addition to nickel-chromium plating, he had been engaged in grinding and polishing and had been chronically exposed to the inhalation of dust containing both nickel and chromium. Sunderman[608] reported a pulmonary carcinoma in a 36-year-old man who had been employed as a polisher and grinder in a nickel-plating workshop and who had been chronically exposed to the inhalation of nickel dust. The interval between first exposure and detection of carcinoma was 9 years. These three case reports suggest the desirability of an epidemiologic study of respiratory-cancer mortality among workers engaged in nickel electroplating and grinding. Such an investigation might be difficult, because nickel plating and grinding are often performed in small factories and workshops.

Histopathology of Respiratory Cancer in Nickel Workers

The histopathology of cases of cancer of the respiratory tract in nickel workers is summarized in Table 6-12, on the basis of observations of Amor,[8] Perry,[475] Løken,[203(p. 209),345] Williams,[716] Morgan (personal communication), Bourasset and Galland,[54] Touraine and Rambaud,[651] and Sunderman.[606] Cancer of the nasal cavities has been reported to originate in the nasal turbinates and in the ethmoid and frontal sinuses. The most common histopathologic types of respiratory cancer in the

TABLE 6-12 Histopathologic Classification of Cancer of the Lung and Nasal Cavities in Nickel Workers[a]

	Lung Cancer		Nasal-Cavity Cancer	
Tumor Classification	No.	%	No.	%
Epidermoid (squamous cell) carcinoma	34	69	22	45
Anaplastic (undifferentiated) carcinoma	13	27	6	12
Alveolar cell carcinoma	1	2	0	0
Adenocarcinoma	1	2	0	0
Columnar cell carcinoma	0	0	2	4
Spheroidal cell carcinoma	0	0	1	2
Spindle cell carcinoma	0	0	1	2
Scirrhus carcinoma	0	0	1	2
Pleomorphic carcinoma	0	0	15	31
Reticulum cell sarcoma	0	0	1	2
TOTALS	49	100	49	100

[a] Derived from Sunderman.[608]

nickel workers have been epidermoid, anaplastic, and pleomorphic carcinomas.

Summary

The cases of cancer of the respiratory tract reported among workmen who were exposed to the inhalation of nickel compounds are summarized in Table 6-13. More than 386 cases of pulmonary cancer and 123 cases of cancer of the nasal cavities have occurred among workers in nickel refineries and factories. The carcinogenic role of nickel cannot be conclusively established in these subjects on epidemiologic grounds, inasmuch as many of the workers were also exposed to the inhalation of other metals, including arsenic, chromium, and cobalt. However, most of the recent authors cited in Table 6-13, as well as other authorities who have reviewed the problem,[261,295,498,524,604,605] have inferred that nickel compounds were the principal carcinogens. Suspicion of carcinogenicity has been focused primarily on respirable particles of nickel, nickel subsulfide, and nickel oxide and on nickel carbonyl vapor. Furnace workers apparently have the highest risk of developing lung cancer, and it is possible that hot, fresh nickel dusts from some roasting processes are especially carcinogenic. Moreover, furnace workers may be subject to combined exposure to nickel compounds and polycyclic hydrocarbon carcinogens, such as benzo[a]pyrene. It is unlikely that any one nickel compound could be implicated as the sole carcinogenic factor, in that cancer of the respiratory tract has occurred at nickel factories and refineries that are involved in diverse metallurgic operations. Furthermore, there are marked variations in the relative proportions of pulmonary cancer and nasal-cavity cancer in workers who are engaged in different industrial processes. Gastric and laryngeal carcinomas and various sarcomas have also been observed in some groups of nickel workers. The possible relations between the nickel that is present in tobacco products, in asbestos fibers, and in implanted prosthetic devices and the development of cancer in man are discussed later in this chapter.

NICKEL CARCINOGENESIS IN EXPERIMENTAL ANIMALS

The experimental systems that have been used to study nickel carcinogenesis in animals are summarized in Table 6-14. Heath and others.[228,229,258,259,410] found that parenteral administration of metallic nickel dust or pellets to rats, guinea pigs, and rabbits results in induction of malignant sarcomas at the injection sites. Gilman[199] has shown that nickel subsulfide (Ni_3S_2) injected intramuscularly into rats is a very potent inducer of rhabdomyosarcomas. Moreover, Gilman (personal communication) has observed epidermoid carcinomas and adenocarcinomas in the sinuses of cats after implantation of nickel sulfide disks. Induction of pulmonary carcinomas in rats has been reported by Hueper[260] after inhalation of nickel dust and by Sunderman *et al.*[587] after inhalation of nickel carbonyl. Lau *et al.*[326] have reported the occurrence of carcinomas and sarcomas in diverse organs (including liver and kidney) of rats that received multiple intravenous injections of nickel carbonyl. Toda[649] and Maenza *et al.*[351] found carcinogenic synergism between some nickel compounds (NiO and Ni_3S_2) and polycyclic aromatic hydrocarbons (methylcholanthrene and benzo[a]pyrene). Thus, nickel carcinogenesis in several species of animals after administration by inhalation or other parenteral routes has been documented. There is no experimental evidence that nickel compounds are carcinogenic when administered orally or cutaneously.[611]

Fifteen nickel compounds have been tested for carcinogenicity after parenteral injection in rats. Table 6-15 compares their valences, solubilities, and relative carcinogenicities.[611] The investigators cited in Table 6-15 used different experimental designs to test carcinogenicity: Payne[466,467] and Friedmann and Bird,[174] single intramuscular implantations; Gilman,[197] bilateral intramuscular injections; and Haro *et al.*[233] and Lau *et al.*,[326] 5–12 intramuscular or intravenous injections at

TABLE 6-13 Cancer of the Lung and Nasal Cavities in Nickel Workers

Major Industrial Processes	Location	Period	References	No. Cases of Lung Cancer	No. Cases of Nasal-Cavity Cancer
Nickel refining (calcination, leaching reduction, and nickel carbonyl process)	Clydach, Wales	1921–1971	[illegible] 125–128, [illegible]	174	78
Nickel refining (calcination, roasting, and electrolysis)	Port Colborne, Ontario	1930–1967	[illegible]	65	23
Nickel refining (sintering)	Copper Cliff, Ontario	1948–1968	[illegible]	27	1
Nickel refining (roasting, leaching, reduction, and electrolysis)	Kristiansand, Norway	1950–1971	[illegible]	51	14
Nickel refining (electrolytic process)	USSR	1959–1965	[illegible]	3	6
Nickel refining (smelting, roasting, and reduction; no electrolysis)	USSR	1955–1967	[illegible]	Unspecified	—
Unspecified	Japan	1957–1959	[illegible]	19	—
Nickel refining (smelting, roasting, and electrolysis)	Aue, Germany	1932–1953	[illegible]	45	—
Nickel plating and polishing (electrolysis and grinding)	France	1960	[illegible]	1	1
Nickel plating and polishing (electrolysis and grinding)	United States	1972	[illegible]	1	—
TOTALS				>386	123

TABLE 6-14 Experimental Models of Nickel Carcinogenesis[a]

Authors	Animals	Substances	Route of Administration	Tumors
Campbell[78]	Mice	Nickel dust	Inhalation	Unspecified
Hueper[218,219]	Rats and rabbits	Nickel dust	Intravenous and intrapleural	Sarcomas
Hueper[209]	Guinea pigs	Nickel dust	Inhalation	Anaplastic and adenocarcinomas
Sunderman *et al*[586,587]	Rats	Nickel carbonyl	Inhalation	Squamous cell carcinomas, anaplastic carcinomas, and adenocarcinomas
Mitchell *et al*[410]	Rats	Nickel pellets	Subcutaneous	Sarcomas
Gilman[190]	Rats and mice	Ni_3S_2 and NiO dusts	Intramuscular	Sarcomas
Toda[668]	Rats	NiO and methylcholanthrene	Intratracheal	Squamous cell carcinomas
Heath *et al*[220,229]	Rats	Nickel dust	Intramuscular	Sarcomas
Haro *et al*[213]	Rats	Nickelocene	Intramuscular	Sarcomas
Gilman (personal communication)	Cats	Ni_3S_2 disks	Sinus implants	Squamous cell carcinomas, adenocarcinomas, and sarcomas
Maenza *et al*[351]	Rats	Ni_3S_2 and benzo[a]pyrene	Intramuscular	Sarcomas
Furst and Schlauder[183]	Hamster	Nickelocene	Intramuscular	Sarcomas
Lau *et al*[320]	Rats	Nickel carbonyl	Intravenous	Carcinomas and sarcomas
Furst and Cassetta[179]	Rats	Nickel dust	Intrathoracic and intraperitoneal	Mesotheliomas
Kasprzak *et al*[291]	Rats	Ni_3S_2 and benzo[a]pyrene	Intratracheal	Squamous cell carcinoma
Kazantis (personal communication)	Rats	Ni_3S_2	Subcutaneous	Fibrosarcomas
Druckrey (personal communication)	Fetal rats	Nickelocene	Transplacental	Malignant neurinoma

[a] Derived from Sunderman.[608]

ERRATA: Some of the data contained in Table 6-15, page 168, *Medical and Biologic Effects of Environmental Pollutants: Nickel*, National Academy of Sciences, 1975, are incorrect. Printed below is the correct version. We suggest you insert this page in its proper position and draw a line through the old page.

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TABLE 6-15 Valences, Solubilities, and Carcinogenicities of Nickel Compounds[a]

			Solubility, mg/ml		Rats with Tumors, %[b]			
Compound	Nickel Valence	Formula	Cold Water[c]	Saline at 37 C[d]	Bethesda Black Rats[466,467]	Fischer Rats[197]	Fischer Rats[223,325]	Sprague-Dawley Rats[178]
Nickel	0	Ni	Insol.	–	–	–	66	23
Nickel biscyclo-pentadiene	0	$Ni(C_5H_5)_2$	Insol.	–	–	–	36	–
Nickel tetracarbonyl	0	$Ni(CO)_4$	0.18	–	–	–	16	–
Nickel subsulfide	0,+,2+	Ni_3S_2	Insol.	<0.001	74	85	–	37
Nickel oxide	2+	NiO	Insol.	0.003	18	10	–	–
Nickel monosulfide	2+	NiS	0.004	–	–	0	–	–
Nickel carbonate	2+	$NiCO_3$	0.093	0.023	40	–	–	–
Nickel hydroxide	2+	$Ni(OH)_2$	0.13	–	–	75	–	–
Nickel fluoride	2+	NiF_2	40	–	–	17	–	–
Nickel acetate	2+	$Ni(C_2H_3O_2)_2$	–	120	7	–	22	–
Nickel hydrated acetate	2+	$Ni(C_2H_3O_2)_2 \cdot 4H_2O$	–	238	5	–	–	–
Nickel sulfate	2+	$NiSO_4$	293	762	0	0	–	–
Nickel chloride	2+	$NiCl_2$	642	1,256	0	–	–	–
Nickel oxide	3+	Ni_2O_3	–	0.001	8	–	–	–
Nickel ammonium sulfate	3+	$NiNH_4SO_4$	–	392	0	–	–	–

[a] Derived from Sunderman.[608]
[b] Compounds administered intramuscularly or intravenously; consult original papers for dosages, vehicles, and durations of observation.
[c] According to Heath.[231]
[d] According to R. C. Weast, Ed. *Handbook of Chemistry and Physics*, 52nd ed., pp. B113–B114. Cleveland: Chemical Rubber Co., 1971.

monthly intervals. There were also significant differences among these studies in strain of rat, injection vehicle, dosage, duration of observation, and method of pathologic examination. Hence, it is impossible to compare directly the tumor incidences that were observed in the five investigations cited in Table 6-15. Nonetheless, there is a general pattern to the data presented there. The carcinogenicities of the nickel compounds appear to be inversely correlated with their solubilities in aqueous media. Thus, the strong carcinogens, nickel subsulfide and nickel oxide, NiO, are practically insoluble in aqueous solutions; and the noncarcinogens—nickel sulfate, nickel chloride, and nickel ammonium sulfate—are highly soluble. There are obvious important exceptions to this rule: nickel monosulfide (which has low solubility) was not carcinogenic in Gilman's study,[7(p. 181)] and nickel acetate (which is relatively soluble) was moderately carcinogenic in the studies by Payne[466,467] and Haro *et al.*[223]

Sunderman *et al.*[611] have reported a controlled experiment in which intramusuclar injection of equimolar quantities of nickel subsulfide, manganese, chromium, copper, and aluminum dusts in Fischer rats resulted in development of sarcomas at the injection site in 96% of rats (23 of 24) that received nickel subsulfide and in 0% of the four similar groups of rats that received the other dusts. This observation negates the possibility that nickel subsulfide induction of sarcomas in rats might constitute a nonspecific reaction to intramuscular injection of any insoluble metallic dust.

Investigations of the carcinogenicity of nickel carbonyl, $Ni(CO)_4$, are summarized in Table 6-16.[611] Particular attention has been focused on nickel carbonyl, owing to its extreme toxicity and its widespread uses as a catalyst in the petroleum, plastics, and rubber industries; as a vehicle for depositing thin films or coatings of nickel in the electronics industry; and as an intermediate product in the Mond process for refining nickel matte in the nickel industry. The studies citied in Table 6-16 demonstrate that cancers are induced in rats after administration of nickel carbonyl by inhalation and by parenteral injection. From an experimental viewpoint, induction of lung cancers in rats by inhalation of nickel carbonyl has three principal advantages: It produces pulmonary carcinomas that closely resemble the lung cancers that develop in nickel workers; because nickel carbonyl is inhaled as a vapor, this method does not entail any problems regarding the influence of particle size on the pulmonary retention of nickel; and because nickel carbonyl is rapidly absorbed by the lung and is distributed throughout the body before being metabolized and excreted in urine and expired air, it is particularly suited for pharmacologic studies. However, inhalation of nickel carbonyl has four

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ERRATA

Some of the data contained in Table 6-16, page 170, *Medical and Biologic Effects of Environmental Pollutants: Nickel*, National Academy of Sciences, 1975, are incorrect. Printed below is the correct version. We suggest you insert this page in its proper position and draw a line through the old page.

TABLE 6-16 Carcinogenesis in Rats by Inhalation or Intravenous Injection of Nickel Carbonyl[a]

Authors	Strain of Rat	Dosage of Nickel Carbonyl	Dosage Schedule	Cancer Incidence	Cancer Locations and Types
Sunderman *et al.*[582,586,587]	Wistar	250 μg/liter per 0.5 h of inhalation	1 exposure	4% lung cancer in 2-yr survivors (vs. 0% in controls)	Anaplastic carcinomas and adenocarcinomas of lung
		30-60 μg/liter per 0.5 h of inhalation	3 times/wk for 1 yr	21% lung cancer in 2-yr survivors (vs. 0% in controls)	Epidermoid carcinomas and adenocarcinomas of lung
Sanna[518]	Not specified	0.7-1.7 μg/liter per 2 h of inhalation	5 times/wk for 2 wk	Not specified	Malignancies in uterus, ovaries, and breasts (including ovarian sarcoma)
Lau *et al.*[326]	Sprague-Dawley	2.2 mg/100 g intravenous	1 injection	8% (vs. 4% in controls)	Carcinoma (kidney), sarcomas (lung and subcutaneous tissue)
		0.9 mg/100 g intravenous	6 injections at 2-4 wk	16% (vs. 4% in controls)	Carcinomas (liver, breast), sarcomas (lung, liver, pancreas, uterus, and subcutaneous tissue)

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[a] Derived from Sunderman.[608]

practical disadvantages as a technique for studying the mechanisms of nickel carcinogenesis: The latent period for induction of lung cancers is long (24–27 months), the incidence of lung cancers is low (4–21% in 2-year survivors), it is necessary to use specialized equipment for inhalation exposures, and stringent safety measures are essential to protect the investigators from accidental poisoning.[608]

Investigations of the induction of sarcomas in rats by intramuscular injections of nickel subsulfide are summarized in Table 6-17. The carcinogenic properties of nickel subsulfide were discovered by Gilman and Ruckerbauer in 1962.[199] They found that a powder collected from the dust flue of a Canadian nickel refinery was a potent carcinogen when injected intramuscularly in rats and mice. By investigating the carcinogenicity of various metallic constituents of the refinery dust (Ni_3S_2, NiO, $NiSO_4 \cdot 6H_2O$, CoS, CoO, CuS, Cu_2S, CuO, FeS, FeO, and Fe_2O_3), Gilman[196] identified nickel subsulfide as the most carcinogenic component. Gilman[196,197] developed one of the simplest, most convenient, and most reproducible methods of chemical carcinogenesis. Induction of sarcomas in Fischer rats by intramuscular injection of nickel subsulfide has proved to be an excellent experimental system for studies of endocrine factors[276,277] and cancer chemotherapy.[182] Several cell lines derived from nickel subsulfide-induced sarcomas have been successfully propagated in tissue culture.[32,33,198,428,444] In 1972, Kasprzak and Marchow published a comprehensive review of experimental carcinogenesis with nickel sulfide.[289]

Table 6-18 summarizes several studies of the induction of sarcomas in rats by intramuscular or subcutaneous injection of metallic nickel in the form of pellets, dust, or sponge. According to Friedmann and Bird, rhabdomyosarcomas induced by metallic nickel are biologically, histologically, and ultrastructurally indistinguishable from rhabdomyosarcomas induced by nickel subsulfide.[174] Heath, Webb, and their coworkers have investigated the subcellular distribution and binding of nickel in rhabdomyosarcomas induced by nickel dust.[229,692] Heath and Webb found that 70–90% of the nickel content of rhabdomyosarcoma cells is present in the nuclei and that the intranuclear nickel is bound to DNA and RNA.[229] Webb and associates have shown that at least 50% of the nickel within rhabdomyosarcoma cell nuclei is in the nucleolar fraction.[692] The possible implications of this intranucleolar localization of nickel in the induction of rhabdomyosarcomas are discussed in the following section. A resume of the biologic characteristics of the sarcomas induced in rats by intramuscular injections of nickel dust or nickel subsulfide is given in Table 6-19, based on the investigations cited in Tables 6-17 and 6-18.

TABLE 6-17 Induction of Sarcomas in Rats by Intramuscular Injection of Nickel Subsulfide[a]

Authors	Strain of Rat	Form and Dose of Nickel Subsulfide	Observations
Gilman and Ruckerbauer[199]	Wistar	Dust, 40 mg	Sarcoma incidence, 89% (80% rhabdomyosarcomas, 20% fibrosarcomas); lung metastases, 76%
Gilman and Herchen[198]	Fischer	Dust, 20 mg Disks, 500 mg Chips, 500 mg	No effect of physical form of nickel subsulfide implant on sarcoma incidence (71-95%) or lung metastases (69-100%)
Gilman and Basrur[195]	Fischer	Dust, 20 mg	Precancerous changes in muscle cells: nucleolar hypertrophy; mitoses; evolution of myoblasts
Jasmin[276,277] and Jasmin *et al.*[278]	Fischer	Dust, 10 mg	Tumor susceptibility not sex-dependent; greatest at age of 2 months; promoted by methandrostenolene
Herchen and Gilman[237]	Fischer	Disks, 250 mg	Tumorigenesis prevented by excision of nickel subsulfide disks within 64 days after implantation
Gilman[197]	Fischer	Dust, 10 mg Disks, 250 mg	Higher sarcoma incidence after intramuscular injection (80%) than after subcutaneous (44%) or intraperitoneal (24%) injection; CaEDTA inhibited muscle tumorigenesis
Daniel[111]	3 strains	Dust, 20 mg	Fischer and hooded rats more susceptible to nickel subsulfide sarcomas than Bethesda black rats
Corbeil[97]	Fischer	Dust, 10 mg	Tumor-specific antibodies in serum from rats with nickel subsulfide sarcomas
Friedmann and Bird[174]	Sprague-Dawley	Dust, 20 mg	Sarcoma incidence, 37%; description of ultrastructure of rhabdomyosarcomas
Herbert *et al.*[231]	Fischer	Dust, 10 mg	Arginase activity much higher in nickel subsulfide rhabdomyosarcomas than in adult or embryonic muscle
Mason[378,379]	Fischer	Dust, 3.3 and 10 mg	At 3.3 mg, mean survival time longer (42 wk) than at 10 mg (36 wk); sarcoma incidence not affected (97% and 85%)
Maenza *et al.*[351]	Fischer	Dust, 20 mg	Sarcoma incidence, 100% (81% rhabdomyosarcomas, 19% fibrosarcomas); lung metastases, 57%; survival time, 33 ± 5 wk
Sunderman *et al.*[611]	Fischer	Dust, 2.5 mg	Sarcoma incidence, 96%; induction of sarcomas by nickel subsulfide antagonized by simultaneous injection of manganese dust
Geissinger *et al.*[188]	Fischer	Dust, 20 mg	Scanning electron microscopy demonstrated chromosomal abnormalities in a nickel subsulfide sarcoma

[a] Derived from Sunderman *et al.*[611]

TABLE 6-18 Induction of Sarcomas in Rats by Intramuscular or Subcutaneous Injection of Metallic Nickel[a]

Authors	Strain of Rats	Form and Dosage of Nickel	Observations
Mitchell *et al.*[415]	Wistar	4 pellets (2 × 2 mm) subcutaneously	Fibrosarcoma incidence, 50%
Heath and Daniel[228]	Hooded	Dust (28 mg) intramusuclarly	Rhabdomyosarcoma incidence, 100%; lymph node metastases, 30%
Heath and Webb[229]	Hooded	Dust (28 mg) intramuscularly	Nickel bound to DNA and RNA in rhabdomyosarcoma nuclei
Friedmann and Bird[174]	Sprague-Dawley	Sponge (20 mg) intramuscularly	Rhabdomyosarcoma incidence, 24%; tumor classification based on differentiation of rhabdomyoblasts
Furst *et al*[182]	Fisher	Powder (5 mg) intramuscularly 6 times at 4-wk intervals	Sarcoma incidence, 76%; latent period, 6–12 months
Webb *et al.*[692]	Hooded	Dust (28 mg) intramuscularly	Intranuclear nickel in rhabdomyosarcoma cells is 53% in nucleolar fraction
Furst and Cassetta[179]	Fischer	Dust (5 mg) intramuscularly 5 times at 4-wk incidence	Sarcoma incidence, 50–75%

[a] Derived from Sunderman.[illegible]

TABLE 6-19 Summary of Biologic Characteristics of Sarcomas Induced in Rats by Intramuscular Nickel Dust or Nickel Subsulfide[a]

Strain susceptibility: Fischer > hooded > Wistar = Sprague-Dawley > Bethesda black
Dosage: Nickel subsulfide at 3.3–20 mg/injection site; nickel at 20–28 mg/injection site
Latent period: 5–10 months
Survival period: 6–12 months
Maximal tumor incidence: 80–100%
Tumor histology: Rhabdomyosarcomas (≈80%), fibrosarcomas (≈20%)
Age of greatest susceptibility: 2 months
Minimal duration of exposure: 2 months
Endocrine factors: No sex difference in susceptibility; promoted by methandrostenolone; depressed by castration and hypophysectomy
Tumor viability: May be transplanted to inbred rats and grown in tissue culture
Metastases: Lungs and lymph nodes (≈50–80%)
Immunology: Serum contains tumor-specific antibodies
Enzymology: Arginase activity in rhabdomyosarcomas higher than in adult or embryonic muscle
Nickel binding: Nickel bound to DNA, RNA, and nucleoprotein and localized particularly in rhabdomyosarcoma nucleoli

[a] Derived from Daniel,[115] Kasprzak and Marchow,[illegible] and Sunderman.[illegible]

POSSIBLE MECHANISMS OF NICKEL CARCINOGENESIS

Elucidating the mechanisms whereby nickel enters the target cells is an important initial step in understanding the mechanisms of nickel carcinogenesis. Owing to its lipid solubility, nickel carbonyl is able to pass across cell membranes without metabolic alteration.[292,618,619] The ability of nickel carbonyl to penetrate intracellularly is presumed to be responsible for its extreme toxicity. Nickel carbonyl decomposes without cells to liberate carbon monoxide and Ni^0, which is oxidized to Ni(II) by intracellular oxidation systems.[618,619] On the basis of the studies of Buu-Hoi *et al.*,[70] it appears likely that nickelocene is also able to penetrate cellular membranes without decomposition and then exert its pharmacologic effects.

A different mechanism must be postulated for the intracellular transport of insoluble inorganic carcinogens, such as nickel dust and nickel sulfide. After intramuscular injection, these compounds are presumed to be deposited extracellularly and to dissolve slowly in the extracellular fluid and muscle autolysate. Singh and Gilman[550] have studied the interaction between rat rhabdomyocytes and nickel subsulfide by use of double-diffusion chambers that were implanted intraperitoneally in adult rats. Explants of embryonic rat skeletal muscle were cultured in one compartment of the double-diffusion chamber, and nickel subsulfide was placed in the adjacent compartment, separated from the muscle cells by a 0.1-μm-pore membrane. Cytologic effects of nickel were detected throughout the period from 2 to 24 days. This study suggests that a diffusible soluble intermediate complex is involved in the intracellular transport of nickel subsulfide. The studies of Heath, Webb, and associates[230,692,693,698] have shown that nickel dust gradually dissolves when incubated aseptically with horse serum to form complexes with serum proteins (50%) and with ultrafiltrable molecules (primarily amino acids, such as histidine). Heath and associates[230,692,693,698] have advanced two alternative hypotheses to account for the cellular penetration of nickel and other metallic carcinogens. In 1969, Heath *et al*[230] suggested that metal–serum protein complexes, adsorbed at the surface of the myoblast, may enter the cells by endocytosis and that later hydrolysis of the carrier proteins by lysosomal proteinases might lead to intracellular release and redistribution of the electrophilic metal ion. In 1972, Webb *et al.*[692,693] suggested as an alternative hypothesis that complexes of nickel with small molecules play key roles as intermediates in the intracellular transport of nickel. They found that nickel dust slowly dissolves when incubated with rat muscle homogenates and that the nickel becomes complexed almost entirely (90%) with ultrafiltrable molecules. Weinzierl and Webb[698] showed that the ultrafiltrable nickel complexes obtained on dissolution of nickel dust in muscle homogenates *in vitro* were similar to those formed when nickel implants slowly dissolved in muscle *in vivo*. They speculated that myoblasts involved in the attempted repair of muscle injury may take up the diffusible nickel complexes and, under the influence of the intracellular nickel, may undergo neoplastic transformation. In support of this speculation, Webb and Weinzierl[693] demonstrated the uptake of diffusible nickel-63 complexes by mouse dermal fibroblasts in tissue culture.

A second step in understanding the mechanisms of nickel carcinogenesis is elucidation of the intracellular biochemical and biologic effects of the Ni^{2+} ions. The biochemical alterations that develop in rats after administration of nickel carbonyl have been investigated by Sunderman *et al*[34,602] in an attempt to identify possible mechanisms of neoplastic transformation. Nickel carbonyl was found to have an inhibitory effect on the induction of several enzymes in lung and liver.[600,602,603,612] As shown in Table 6-20, nickel carbonyl did not affect substrate (tryptophan) induction of hepatic tryptophan pyrrolase, but did impair cortisone induction of tryptophan pyrrolase; this suggests that nickel carbonyl may produce a metabolic block at the level of messenger RNA.[602] Nickel carbonyl also inhibited phenothiazine induction of hepatic benzopyrene hydroxylase[600] and phenobarbital induction of hepatic cytochrome P_{450} and aminopyrine demethylase.[612]

TABLE 6-20 Acute Biochemical Effects of Nickel Carbonyl in Rats[a]

Experimental System	Observed Activities, % of control values[b]	
	Control Rats	$Ni(CO)_4$-Treated Rats[c]
Hepatic tryptophan pyrrolase activity after tryptophan induction	100 ± 17 (7)	100 ± 12 (7)
Hepatic tryptophan pyrrolase activity after cortisone induction.	100 ± 6 (27)	72 ± 7* (9)
Hepatic benzopyrene hydroxylase activity after phenothiazine induction	100 ± 8 (25)	45 ± 8* (9)
Hepatic cytochrome P_{450} concentration after phenobarbitone induction	100 ± 4 (16)	48 ± 5* (9)
[^{14}C]leucine incorporation *in vivo* into hepatic microsomal protein	100 ± 5 (16)	82 ± 6* (11)
[^{14}C]orotic acid incorporation *in vivo* into hepatic RNA	100 ± 14 (9)	25 ± 2* (8)
RNA polymerase activity in intact hepatic nuclei	100 ± 6 (7)	40 ± 7* (8)
RNA synthesis *in vitro* by chromatin–RNA polymerase complex from hepatic nuclei	100 ± 9 (18)	49 ± 6 (18)
Template activity of hepatic chromatin for RNA polymerase from *Micrococcus lysodeikticus*	100 ± 9 (6)	87 ± 12 (5)
Template activity of hepatic DNA for RNA polymerase from *M. lysodeikticus*	100 ± 12 (6)	98 ± 6 (5)

[a] Derived from Sunderman.

[b] Expressed as mean ± SEM, with number of rats in each experiment group in parentheses; values marked with an asterisk differ significantly from the control values ($p < 0.01$).

[c] $Ni(CO)_4$ administered intravenously at 2.2 mg/100 g of body weight 6–28 h before sacrifice.

These findings led to studies of the effects of nickel carbonyl on hepatic synthesis of RNA and proteins. At 24 h after injection of a dose of nickel carbonyl equivalent to the LD_{50}, there was 60% inhibition of DNA-dependent RNA polymerase activity in hepatic nuclei[610] and 75% inhibition of RNA synthesis, as measured by incorporation of [^{14}C]orotic acid into RNA.[38] Under identical experimental conditions, nickel carbonyl produced only 18% reduction of hepatic protein synthesis, as measured by incorporation of [^{14}C]leucine into microsomal proteins.[598] Beach and Sunderman[39] showed that exposure of rats to nickel carbonyl inhibited RNA synthesis *in vitro* by a chromatin–RNA polymerase complex that was prepared from hepatic nuclei. This study demonstrated that nickel carbonyl inhibition of RNA synthesis persists after disruption of the nuclei and thereby excluded inhibition, owing to impaired transport of RNA precursors across the nuclear membrane. Independent confirmation of the inhibitory effect of nickel carbonyl on hepatic RNA synthesis has been furnished by Witschi.[718] Beach[37] has found that administration of nickel carbonyl did not significantly impair the template activity of isolated rat liver chromatin or DNA for transcription by RNA polymerase from *Micrococcus lysodeikticus*. The lack of an inhibitory effect of nickel carbonyl on the template activities of rat liver chromatin and DNA may possibly be ascribed to elution of nickel during isolation of the chromatin and DNA.[37]

Webb and co-workers[692] have studied the intracellular distribution of nickel in nickel-induced rhabdomyosarcomas and have found that a major portion (70–90%) of the nickel is within the nucleus. Furthermore, subfractionization indicated that an average of 53% (range, 41–63%) of nuclear nickel is present on the nucleolar fraction.[692] The remainder of the nuclear nickel is distributed approximately equally between the nuclear sap and the chromatin fractions. Nucleolar localization of nuclear nickel has also been observed by Webb and Weinzierl[693] in mouse dermal fibroblasts grown *in vitro* in the presence of nickel-63 complexes. Intracellular nickel-63 in the fibroblasts was predominantly within the nuclei, and half the nuclear nickel-63 was associated with the nucleolar fraction.[693] Webb and co-workers[692] emphasized the possible relations between their findings of nucleolar localization of nickel in rhabdomyoblasts and fibroblasts and the findings of Beach and Sunderman[39] that nickel is bound to an RNA polymerase–chromatin complex isolated from hepatocyte nuclei of rats that were treated with nickel carbonyl.

Buu-Hoi *et al.*[70] have shown that administration of nickelocene in rats prolongs paralysis induced by zoxazolamine and potentiates the anticoagulant effects of Tromexan. The mechanism of nickelocene inhibition of metabolism of zoxazolamine and Tromexan has not been explained,[70] but it is presumed to resemble the inhibitory effects of nickel carbonyl on hepatic enzyme induction.[600,602,603,612] Treagan and Furst[652] have shown that addition of nickel chloride to tissue cultures of mouse L-929 cells inhibits their capacity to synthesize interferon and antiviral protein in response to inoculation with Newcastle disease virus. Hence, if one assumes that oncogenes of RNA tumor viruses are the basic determinants of many types of cancer,[256] it can be speculated that nickel may temporarily inhibit synthesis of a product of the host genome that normally causes repression of the viral oncogene. According to the Huebner–Todaro hypotheses,[256] expression of the viral oncogene would then lead to the development of cancer. Basrur and Gilman[33] and Swierenga and Basrur[625] have shown that addition of nickel sulfide to cultured embryonic muscle cells inhibits mitotic activity and induces abnormal mitotic figures. Their findings suggest that nickel may interfere with gene replication and with the control of cell division.

Current theories regarding possible mechanisms whereby chemical carcinogens may initiate neoplastic transformation are summarized in Table 6-21,[608] on the basis of Miller and Miller's 1971 schema[497] with modifications derived from Ryser,[587] Weinstein *et al.*,[697] and Jungmann and Schweppe.[286] The studies of nickel carcinogenesis reported by Sunderman and associates[39,602] and by Heath, Webb, and co-workers[230,693] are most consistent with hypotheses I-C, II-A, and II-B; the studies of Treagan and Furst[650] appear to support hypothesis II-B; and the studies of Gilman, Basrur, and Swierenga[33,625] are most consistent with hypotheses I-A and I-B. Thus, despite considerable speculation,[178,180,181,714] there is currently little understanding of the exact mechanisms whereby nickel compounds exert their carcinogenic actions.

From a methodologic viewpoint, nickel carcinogenesis affords an especially attractive experimental model for further research into mechanisms of chemical carcinogenesis, inasmuch as the carcinogenic nickel compounds are structurally simple, inexpensively available in high purity, and readily labeled with nickel-63, a beta-emitting radioisotope with a long half-life, which is ideally suited for liquid scintillation spectrometry and autoradiography.[608]

RELATION OF NICKEL CARCINOGENESIS TO OTHER FACTORS

Nickel in Tobacco Products

The amount of nickel in cigarettes has been measured by seven independent groups of investigators. As summarized in Table 6-22, the reported mean nickel contents of cigarettes from various sources have ranged from 2.0 to 6.2 μg/cigarette. Analyses by Sunderman and Sunderman,[595] Szadkowski and co-workers,[628] and Stahly[560] have shown that 10–20% of the nickel in cigarettes is released into the mainstream smoke. On the basis of the measurements summarized in Table 6-23, a person who smokes 40 cigarettes/day might inhale approximately 1–5 mg of nickel per year. According to Szadkowski and associates,[628] an average of 84% of the nickel in mainstream smoke is in the gaseous phase and only 16% in the particulate phase. Sunderman and Sunderman[595] speculated that gaseous nickel in mainstream smoke occurs in the form of nickel carbonyl. Furst[177] and Wynder and Hoffman[722] objected to this suggestion, on the grounds that nickel carbonyl would readily decompose in tobacco smoke. This objection has been weakened by evidence[292,618] that nickel carbonyl is more stable in air, breath, and biologic fluids than had previously been suspected.

Suggestive evidence that the gaseous nickel in cigarette smoke is nickel carbonyl has recently been reported by Stahly,[560] who found that, during the smoking of cigarettes, nickel was partially vaporized from the cooler parts of cigarettes. Stahly demonstrated that passing metal-free carbon monoxide gas at 20–100°C through the tobacco before smoking removed much of the nickel. Nickel was recovered in a gray-black film that formed in a glass tube when the effluent stream was heated to 400°C. Stahly concluded that the removal of nickel from tobacco by carbon monoxide gas lends credence to the presence of nickel carbonyl in tobacco smoke.

Measurements of the nickel in various other tobacco products are listed in Table 6-24. American pipe tobacco, cigars, and snuff have been reported to contain nickel at approximately 2–3 μg/g of tobacco. Fresh and associates[172] have found that Formosan cigars contain an average of 8.5 μg/g. Baumslag and co-workers[35] have found that three varieties of South African "Swazi" snuff are grossly contaminated with nickel and other metals. Swazi snuff consists of an admixture of powdered tobacco with the ash of incinerated herbs. On the basis of epidemiologic evidence, Baumslag *et al.*[34,35] have suggested that nickel and other metals in Swazi snuff may contribute to the prevalence of carcinomas of the nose and accessory sinuses among Bantu males. Langer and associates[324] have demonstrated diatom crystals and other inorganic particles in the mainstream smoke of cigars that are wrapped with sheets of reconstituted tobacco. Reconstituted tobacco sheets are used primarily in inexpensive cigars and may contain up to 40% of additives, including minerals (bentonite, montmorillonite, acid-treated clays, and diatomaceous earths), which may potentially contain traces of nickel and other metals. No data are yet available con-

TABLE 6-21 Current Hypotheses Regarding Chemical Induction of Carcinogenesis[a]

I. Genetic Mechanisms	II. Epigenetic Mechanisms
A. Direct modification of existing DNA ("somatic mutation"), in which replication of chemically altered DNA causes inheritable modifications, deletions, or rearrangements of the DNA nucleotide sequence, causing permanent changes in growth regulation	*A. Chemical modification of RNA or proteins* (e.g., histones and nuclear acidic proteins) that regulate DNA template activity, causing expression of normally repressed portions of the DNA genome
B. Alterations of DNA polymerase, which temporarily decrease the fidelity of DNA replication, causing mutations of the DNA genome	*B. Chemical modification of RNA or proteins*, causing depression of tumor viruses or oncogenes
C. Chemical modification of RNA, which is later transcribed into DNA that becomes integrated in the host genome; this may involve viral RNA-primed DNA polymerase ("reverse transcriptase")	*C. Carcinogen-induced changes in immunologic or hormonal mechanisms*, leading to preferential proliferation of previously existing preneoplastic or neoplastic cells

[a] Modified from Miller and Miller.[illegible]

TABLE 6-22 Nickel Content of Cigarettes

Authors	Source of Cigarettes	No. Brands	Mean Nickel Content, μg/cigarette[a]
Coghill and Hobbs	United States	5	2.0
Voss and Nicol	England	11	6.2 (3.6–11.0)
Sunderman and Sunderman	United States	6	2.2 (1.6–3.1)
Fresh *et al.*	United States	15	5.4 (0.2–11.6)
	Formosa	12	4.3 (1.1–14.0)
Szadkowski *et al.*	Germany	8	2.3 (1.1–3.2)
Menden *et al.*	United States	2	5.9 (4.3–7.6)
Stahly	United States	1	4.4

[a] Numbers in parentheses are ranges.

cerning the nickel content of mainstream smoke from cigars that are wrapped with such sheets of reconstituted tobacco.

Nickel in Asbestos

Investigations by Harington,[221] Dixon *et al.*,[122,123] Cralley *et al.*,[102,103] Gross *et al.*,[210] Holmes *et al.*,[252,253] and Roy-Chowdhury *et al.*[501] have demonstrated the occurrence of nickel—with generally smaller quantities of cobalt, chromium, and manganese—in several varieties of asbestos and have implicated these metals as possible etiologic factors in asbestos carcinogenesis. The metal contents of the asbestos fibers are attributable primarily to minerals that are naturally associated with the asbestos. To a minor extent, the metal contents may also derive from abrasion of metal alloys in the asbestos grinding and processing equipment. The analyses summarized in Table 6-25 indicate the concentrations of nickel reported to occur in several varieties of asbestos from Africa and Canada. On the basis of measurements of airborne concentrations of nickel in seven asbestos plants in the United States, Cralley and co-workers[103] have speculated that atmospheric nickel and other metals might constitute a carcinogenic hazard in the working environment. In a study of metal exposures of workers mining and milling asbestos in Quebec, Gibbs *et al.*[193] found average mill airborne dust concentrations of nickel to range from 16 to 42 μg/m^3.

Holmes *et al.*[252,416] induced radioactivity in metals in asbestos fibers by neutron irradiation and then traced metal translocations in rats after administration of the radioactive asbestos by intrapleural injection. They demonstrated conclusively that chromium and cobalt are rapidly leached from crysotile asbestos fibers *in vivo*. After 50 days, 19% of administered

TABLE 6-23 Partition of Nickel During Cigarette Smoking[a]

Authors	Cigarettes	Nickel Content, μg/cigarette (mean ± SD) Total	Ash and Butt	Mainstream Smoke	Gaseous Phase	Particulate Phase
Sunderman and Sunderman[595]	1 U.S. brand	1.85 ± 0.22	1.32 ± 0.23	0.37 ± 0.16		
Pailer and Kuhn[457]	1 Austrian brand			0.1		
Szadkowski *et al.*[528]	8 German brands[b]	2.340 ± 0.650	1.140 ± 0.780	0.225 ± 0.142	0.190 ± 0.140	0.035 ± 0.024
Menden *et al.*[397]	Kentucky reference cigarettes	4.25 ± 0.18	3.14	[c]	[c]	0.08
	1 U.S. commercial brand	7.55 ± 0.50	6.71	[c]	[c]	0.02

[a] Derived from Sunderman.[608]

[b] Including five brands of cigarettes with filters.

[c] Menden *et al.*[397] measured nickel in the particulate phase, but they neglected to measure nickel in the gaseous phase.

TABLE 6-24 Nickel Content of Various Tobacco Products[a]

Authors	Product	Source of Product	No. Varieties	Mean Nickel Content, μg/g[b]
Sunderman and Sunderman[595]	Pipe tobacco	United States	1	2.7
	Cigars	United States	1	3.2
Fresh *et al.*[172]	Cigars	Philippines	3	2.8 (1.9–3.9)
	Cigars	Formosa	3	8.5 (3.6–15.0)
Baumslag *et al.*[35]	Snuff	United States	3	2.3 (2–3)
	Snuff	South Africa	3	52 (43–87)
Baumslag and Keen[34]	Snuff	South Africa	3	88 (58–112)
Stahly[560]	Cigarette and pipe tobacco	United States	12	No mean (0.5–10.0)

[a] Derived from Sunderman.[608]
[b] Numbers in parentheses are ranges.

TABLE 6-25 Nickel Concentrations in Samples of Asbestos

			Nickel Content, µg/g			
Authors	Date	Origin of Asbestos	Crocidolite	Anthophyllite	Amosite	Chrysotile
Harington[221]	1965	Africa	<10		80	5,000
Gross *et al.*[210]	1967	Canada				135
Cralley *et al.*[103]	1967	Africa	<100		<100	1,400
		Canada				1,000
Jagatic *et al.*[274]	1967	Not specified				4,000
Cralley *et al.*[102]	1968	UICC reference samples (particle size, <10 µg)	139	414	105	1,676
Holmes *et al.*[253]	1971	Africa	<100	1,360	<100	1,250
		Canada				550–2,600
Reeves *et al.*[494]	1971	Not specified[a]	70–73		40	222–294
		Not specified[b]	88–111		97–108	374–461
		UICC reference samples	13–100		34	795–990
Roy-Chowdhury *et al.*[502]		Crude commercial	12 ± 1		52 ± 2	30 ± 40
						880 ± 80
		UICC reference samples	12 ± 2		36 ± 2	700 ± 60

[a] Raw asbestos, as shipped by manufacturer.

[b] Processed asbestos, as collected on Millipore filters in inhalation chambers.

chromium-51 and 57% of cobalt-60 had been excreted in the urine.[252] Cralley[101] has observed that such metals as chromium and manganese, which are present in asbestos fibers and which are higher than nickel in the electromotive series, suppress the solubilization of nickel by bovine serum *in vitro*. Cralley has advanced a hypothesis for metal interactions in asbestos carcinogenesis based on electromotive phenomena, has speculated that the asbestos fiber serves as a transport mechanism for introduction of metals and minerals into the tissues of the body, and has proposed that the presence in asbestos of such metals as chromium and manganese enhances the carcinogenicity of the nickel, which also occurs in asbestos. Cralley's speculations furnish a testable hypothesis that may help to elucidate the mechanisms of asbestos carcinogenesis.

Nickel in Medications

Early reports of the use of nickel-containing medications in man are summarized in Chapter 1. Geschickter and Reid[189] administered nickel monobutylphthalate in attempted chemotherapy of human leukemia and lymphoma. Henkin and Bradley[236] administered nickel acetate orally in a successful attempt to alleviate hypogeusia in a patient with multiple myeloma. Butler *et al.*[67] reported beneficial clinical trials of the nickel chelate of tetramethylphenanthroline for topical use in prophylaxis of staphylococcal infections in newborn infants, in adolescents with acne vulgaris, and in women undergoing gynecologic surgery. Weisburger[700] has cautioned that extensive clinical use of such nickel chelates as topical bactericidal drugs should be deferred until adequate animal tests for carcinogenicity have been performed.

Nickel Devices and Prostheses

Nickel-containing alloys have been implanted in man and animals in a wide variety of therapeutic devices and prostheses, including stainless-steel and nickel wires as suture materials,[721] nickel–chrome metallic mesh for nasal prostheses,[427] stainless-steel heart-valve prostheses,[520] nickel-containing intrauterine contraceptive devices,[81,299,450] nickel–cadmium batteries for implantable cardiac pacemakers,[240] and nickel alloys[219,324,551] for dental castings and filling material and orthopedic implants.[29,130,225,389]

Although it has generally been assumed that nickel in stainless steels is biologically inert, Ferguson and co-workers[151] have reported that intramuscular implantation of cylinders of stainless steel (Incoloy—stainless steel #316—and stainless steel #A-286) in rabbits resulted in increased nickel concentrations in parenchymal tissues. Moreover, Mears[395] has demonstrated by electron microprobe analysis that nickel is liberated into human tissues adjacent to implants of stainless-steel rods (stainless steel #316, containing 8% nickel, 18% chromium, and 3% molybdenum). The nickel concentration was consistently highest at the tissue edge adjacent to the implant. Mears[395] has also found that tissue-culture cells (fetal rat dermal fibroblasts) that were grown on grids of stainless steel #316 accumulated nickel that was clearly demonstrable by electron microprobe analysis. Mears[395] concluded that stainless steel #316 yielded nickel corrosion products in the interstitial fluid, which in turn became associated with the tissue-culture cells.

There is a paucity of evidence concerning the possible carcinogenicity of implanted nickel alloys in experimental animals. Mitchell *et al.*[410] implanted four pellets of nickel–gallium dental filling material (60% nickel and 40% gallium) subdermally in Wistar rats and found that sarcomas developed at one or more implantation sites in nine of 10 rats. For comparison, local sarcomas developed in five of 10 rats that received implants of pure nickel. No sarcomas developed in any of 10 other experimental groups of 10 rats each, which received implants of diverse other materials that have been used in dentistry. According to Hueper,[257] "the evidence on hand indicates that metal implants which contain nickel and which remain over long periods in human tissues might create delayed potential cancer hazards to their recipients."

Two published clinical case reports support Hueper's warning. In a patient described by McDougall,[386] a sarcoma developed in the soft tissues of an arm 30 years after implantation of a steel plate. In a patient described by Dube and Fisher,[130] a hemangioendothelioma developed in a tibia 30 years after implantation of a steel plate. In both patients, the implanted steel plate was fabricated of an alloy that differed from that of the screws used to fix the plate *in situ*. Such conjoined surgical implantation of metals of dissimilar composition may result in unnecessary electrolysis and metallic corrosion.[130] Dube and Fisher speculated that metallic corrosion products, including nickel and chromium, were responsible for the induction of the hemangioendothelioma in their patient.

Interrelations of Nickel with Polycyclic Aromatic Hydrocarbons

Possible carcinogenic interrelations between nickel compounds and polycyclic aromatic hydrocarbons have been suggested by physicians who have had long experience in the nickel industry.[128] On the basis of their clinical observations, it is suspected that workers in nickel refineries who are heavy cigarette smokers are particularly prone to development of cancers of the lungs. Doll *et al.*[128] have hypothesized that differences in the amount of cigarette smoking among nickel workers affect the incidence of lung cancer, but not of nasal sinus cancer. Unfortunately, it has not yet been possible to obtain epidemiologic evidence to test this hypothesis.

Experimental support for speculations regarding carcinogenic synergism between nickel compounds and polycyclic aromatic hydrocarbons has been furnished by carcinogenesis studies in animals[351,649] and by biochemical studies of the effects of nickel compounds on the metabolism of benzo[a]pyrene.[122,599,617] Toda[649] has found that five of 30 rats (17%) that received intratracheal injections of nickel oxide in combination with 20-methylcholanthrene developed pulmonary neoplasms (squamous cell carcinomas).

Maenza *et al.*[351] have observed that the latent period between administration of carcinogen and development of sarcomas was significantly shorter (by 30%) in rats that received intramuscular injections of a combination of nickel sulfide and benzo[a]pyrene than in rats that received only one or the other. Their findings were consistent with carcinogenic synergism, rather than an additive effect, inasmuch as such diminution of the latent period was not achieved by increasing the dosage of nickel sulfide or benzo[a]pyrene when administered singly, rather than in combination.

Sunderman[599] has reported that exposure of rats to nickel carbonyl by inhalation or intravenous injection inhibited the induction of benzopyrene hydroxylase activity in lung and liver. Benzopyrene hydroxylase is a microsomal enzyme that converts carcinogenic benzo[a]pyrene to noncarcinogenic hydroxylated metabolites. Nickel carbonyl inhibition of benzopyrene hydroxylase activity was apparently mediated by diminished synthesis of the enzyme, inasmuch as nickel carbonyl did not directly inhibit benzopyrene hydroxylase activity *in vitro* after addition to enzyme reaction mixtures in final concentrations up to 10^{-4} *M*.[4] Dixon *et al.*[122] have found that nickel directly inhibits benzopyrene hydroxylase activity in microsomes from rat and human lungs, if nickel sulfate is added *in vitro* to enzyme reaction mixtures in final concentrations greater than 10^{-3} *M*. Sunderman[599] and Dixon *et al.*[122] suggested that nickel might promote carcinogenesis by inhibiting benzopyrene hydroxylation and prolonging tissue retention of benzo[a]pyrene. Sunderman and Roszel[617] have reported experimental evidence in support of this hypothesis. They administered benzo[a]pyrene to rats by intravenous injection and studied the effect of a single exposure to nickel carbonyl on the retention of benzo[a]pyrene in lung and liver. Their results demonstrated that exposure to nickel carbonyl inhibited the mobilization of benzo[a]pyrene from lung and liver for 48 h.[617] Kasprzak *et al.*[291] observed that the incidence of premalignant pathologic reactions in the lungs of rats that received an intratracheal injection of a combination of nickel subsulfide and benzo[a]pyrene was significantly greater than in the lungs of rats that received only nickel subsulfide or benzo[a]pyrene. The premalignant pathologic reactions included peribronchial adenomatoid proliferation and bronchial squamous metaplasia. One squamous cell carcinoma of the lung was observed in the group of 12 rats that received the combination of nickel subsulfide and benzo[a]pyrene. Pulmonary cancers were not found in the other experimental groups.

The experimental evidence cited appears to furnish sufficient justification for a careful epidemiologic study of the association of lung cancer with cigarette smoking among workmen in nickel refineries. Similar carcinogenic interactions between industrial exposures to minerals and cigarette smoking have already been demonstrated in asbestos workers[538] and in uranium miners.[348] It may be noted that Park and co-workers[462] are investigating the cocarcinogenicity of inhaled nickel oxide and cigarette smoke in hamsters.

Possible Interrelations of Nickel with Parasites and Viruses

A report by Keller *et al.*[296] that infestation with *Nippostrongylus brasiliensis* promotes the development of transplantable tumors in rodents stimulated Kasprzak *et al.*[290] to study the effect of infestation with *Trichinella spiralis* on the induction of sarcomas in rats after intramuscular injection of nickel sulfide. Kasprzak *et al.*[290] found that administration of *T. spiralis* larvae in rats 5 days before the injection of nickel sulfide significantly increased the incidence of rhabdomyosarcomas. This observation merits confirmation, for it may adumbrate a hitherto unsuspected carcinogenic synergism.

Treagan and Furst[652] have reported that addition of nickel chloride to tissue-culture medium profoundly inhibits the capacity of mouse L cells to synthesize interferon after exposure to Newcastle disease virus. Moreover, the antiviral activity of the interferon that was formed in the nickel-treated cells was found to be only approximately one-fifth that of the interferon formed in untreated cells. These observations also deserve confirmation, for they may suggest a mechanism whereby exposures to nickel could facilitate the replication of tumor viruses.

7

Nickel in the Reproductive System

There are very few published reports on the effects of nickel on reproductive processes, and little is known about its possible mutagenic effects. Phatak and Patwardhan[480] reported in 1950 that nickel fed in the diet of rats at 250, 500, and 1,000 ppm in three different forms did not have any significant effects on reproduction. Their limited data, however, suggest that litter size was reduced at the highest concentration. Whole-body analyses of offspring at birth disclosed nickel at 22–30 ppm in offspring of mothers given nickel carbonate at 1,000 ppm in the diet and 12–17 ppm in offspring of mothers given 500 ppm. Offspring of mothers given nickel catalyst at 1,000 ppm contained nickel at only 1.2–4.4 ppm. Nickel in this form was apparently poorly absorbed, inasmuch as 90% of the intake was excreted in the feces.

Adverse effects on reproductive processes have been reported in rats after administration of soluble nickel salts. Hoey[249] studied the acute and chronic effects on rat testes of nickel sulfate given subcutaneously at 0.04 millimole/kg. Shrinkage of central tubules, hyperemia of intertubular capillaries, and disintegration of spermatazoa were observed 18 h after a single dose. The effects of multiple doses were an extension of the acute effects (including further shrinkage of tubules), disintegration of spermatocytes and spermatids, and cytotoxic effects on Sertoli's cells. These effects were reported to be nearly completely reversible. Inhibition of spermatogenesis has also been observed after oral administration of daily doses of nickel sulfate at 25 mg/kg.[681] Reduction in the number of basal cells within the tubules and in the number of tubules that contained spermatazoa was reported. Male rats given nickel sulfate at 25 mg/kg per day for 120 days were apparently infertile, inasmuch as no pregnancies resulted when the males were caged with females in estrus.

Soluble nickel salts administered in the drinking water also produced adverse effects on reproduction in rats.[530] Young rats of the Long-Evans strain were paired and given drinking water containing nickel at 5 ppm continuously over three generations. The average litter size declined with each succeeding generation, and offspring mortality was significantly increased over that in the control group. The number of runts was also significantly increased in each succeeding generation. In addition, fewer males than normal were born in the third generation, resulting in a lowered male : female ratio.

Exposure of rainbow trout eggs and sperm to nickel sulfate at a nickel concentration of 1.0 mg/liter for 30 min had no effect on percentage of fertilization or hatchability. However, the rate of development of the exposed eggs was increased, so most had hatched before any of the control eggs had. The significance of this reduced hatching time is not known, because later effects on growth and viability were not reported.[540]

8

Summary and Conclusions

The Panel on Nickel has assembled, studied, and discussed all the available data that pertain to nickel in the environment and its effects on man and animals. Consideration has been given to the natural sources of nickel, the production of nickel from its ores, the manufacturing processes that use nickel, the recycling of nickel in the biosphere, occupational hazards from nickel, community exposures to nickel, and experimental studies in animals that are related to the metabolism, toxicity, carcinogenicity, and mutagenicity of nickel and its compounds. Attention has also been directed to the biochemical ligands that react with nickel *in vitro* and *in vivo* and to methods of analyzing nickel in biologic and environmental samples. This report summarizes 2 years of deliberations by the Panel on Nickel.

Nickel, like many other trace elements, is widespread in the contemporary human environment. Because nickel is present in natural waters and in practically all soils and foods, man is inevitably subject to oral and cutaneous exposures to trace amounts of nickel compounds. Man is not naturally exposed to the inhalation of atmospheric nickel, with the possible exception of nickel from volcanic emanations. The available evidence indicates that the natural concentrations of nickel in waters, soils, and foods do not constitute a biologic threat. Indeed, nickel may be an essential trace element for the nutrition of man and animals.

Man normally ingests nickel in food and water at an estimated 300–600 μg/day. Most of the ingested nickel is excreted in the feces, but a small proportion is absorbed and later excreted in the urine, bile, and sweat. Numerous complexes of nickel with biochemical molecules have been studied *in vitro*. Although knowledge of nickel binding *in vivo* is limited, there is evidence that nickel is associated with diverse biologic substances, including proteins, amino acids, and possibly nucleic acids. Disturbances of nickel metabolism occur in some common diseases of man, such as myocardial infarction and stroke.

Man's use of nickel and nickel-containing materials has been steadily increasing in recent years, and it is therefore probable that nickel concentrations in ground and surface waters and in the atmosphere will continue to increase. Increased amounts of nickel in the biosphere should be viewed with caution. Emissions from the combustion of fossil fuels, principally coal and petroleum, are a major source of atmospheric nickel. Persons who reside in urban areas are exposed to inhalation of nickel, owing to atmospheric contamination from industrial emissions. Inhalation exposure of man to nickel compounds also occurs as a consequence of tobacco smoking, inasmuch as a portion of the nickel in tobacco is released into mainstream tobacco smoke.

Toxicity studies have demonstrated that nickel and nickel salts have relatively low toxicity in various species of animals when administered orally. However, parenteral injections of nickel salts are much more toxic. Major signs of acute nickel toxicity consist of hyperglycemia and gastrointestinal and central nervous system effects. Ingested nickel is excreted primarily in the feces, whereas parenterally administered nickel is excreted mostly in the urine. Little information is available on animals relative to the acute effects of inhaled nickel compounds, except for nickel carbonyl, which is extraordinarily toxic. Accidental industrial exposure to inhalation of nickel carbonyl can be prevented by careful plant design, continuous atmospheric measurements, monitoring of nickel concentrations in body fluids, and the use of protective clothing and respirators. The major therapeutic agents for nickel carbonyl poisoning in man are chelating drugs, such as sodium diethyldithiocarbamate. Several nickel-containing substances—including nickel dust, nickel subsulfide, nickel oxide, nickel carbonyl, and nickel biscyclopentadiene—have been demonstrated to be carcinogenic in experimental animals after inhalation or parenteral administration. There is no evidence that nickel compounds are carcinogenic in animals after oral or cutaneous exposure. There is very little information on the teratogenicity or mutagenicity of nickel compounds in experimental animals.

Epidemiologic studies of workmen in nickel smelters and refineries have revealed a significantly increased incidence of cancers of the lungs and nasal cavities. Increased risk of respiratory neoplasia appears to be especially associated with specific operations involving roasting and conversion of nickel sulfide to nickel oxide. Respiratory cancers in nickel workers have usually developed after long latent periods, such as are typical of occupational cancers. The technology of nickel smelting and refining has undergone changes that probably have diminished the risk of respiratory carcinogenesis. There is only scanty evidence of an increased incidence of respiratory cancers among workmen who have other types of occupational exposure to nickel, such as nickel electroplating and grinding. The nickel that is present in asbestos may possibly contribute to the carcinogenicity associated with asbestos inhalation in man.

Nickel is a common cause of chronic dermatitis in man, as a result of industrial and other exposures. As a consequence of the use of nickel-containing alloys in jewelry, coinage, clothing fasteners, and utensils, there is widespread cutaneous exposure of the general populace to nickel. Of special significance is the recent observation that nickel in implanted therapeutic devices and prostheses can be responsible for dermatitis.

9

Recommendations

On the basis of its deliberations, the Panel on Nickel makes the following specific recommendations:

1. *Monitoring Airborne Nickel.* Methods of air sampling and analysis for nickel should be standardized, to permit reliable comparisons of data from different collection sites. Stations for air sampling and nickel analysis should be established throughout the country to monitor the emission of nickel from industrial stacks. These efforts should be directed not only to measurements of the quantity of nickel released, but also to determinations of its chemical form and of the size distribution of nickel-containing particles. Air sampling and nickel analysis should be applied to the exhausts from calciners, refineries, and alloy melting furnaces. Measurements of airborne nickel should also be made in the vicinities of welding, electroplating, grinding, buffing, and polishing operations to quantitate occupational exposure to airborne nickel. Direct measurements of nickel in emissions from stationary and mobile power sources should be made to quantitate these sources of atmospheric nickel.
2. *Industrial Health and Safety.* Industries that use nickel or its compounds should maintain comprehensive health records on employees who are engaged in nickel-processing activities—such as mining, concentrating, refining, smelting, casting, hot-working, fabricating, plating, or

machining—or the use of nickel catalysts. The exposure of workers to nickel-containing dusts and fumes should be minimized, and special attention should be given to ventilation and dust control in industrial plants where nickel is refined or processed. Workers in nickel production, refining, and processing facilities should stringently avoid inhalation of nickel-containing dusts. The oxidation of nickel sulfides to oxides and industrial operations that use nickel carbonyl should be viewed with particular concern and should be conducted in closed systems. Industries that use nickel carbonyl should monitor the atmospheric concentration of nickel carbonyl, perform routine analyses of nickel concentrations in body fluids from potentially exposed workers, and ensure that effective therapeutic measures for acute poisoning from nickel carbonyl are immediately available.

3. *Epidemiologic Investigations.* Detailed epidemiologic investigations should be initiated or continued to ascertain whether any risk of respiratory carcinogenesis is currently associated with nickel refining processes and exposure to nickel carbonyl. The possible relation of cigarette smoking to respiratory carcinogenesis in nickel workers needs to be elucidated. A registry of nickel-associated cancers should be established to compile relevant data from industrial and public-health authorities throughout the world. Epidemiologic studies should be undertaken to assess the health of the general public in communities near nickel refineries.

4. *Toxicology of Nickel Compounds.* A thorough reassessment of the toxicology of nickel and its compounds in experimental animals should be undertaken. The toxicologic advantages and disadvantages of nickel compounds should be evaluated in relation to other metallic compounds that could be used for similar purposes. Comparisons should be made of the toxic effects of tetrahedral, octahedral, and planar nickel compounds. Toxicologic investigations of nickel compounds should include long-term studies in several animal species to evaluate carcinogenesis, teratogenesis, and mutagenesis. The carcinogenesis studies should include investigations of nickel carbonyl exposure in dogs and primates and carcinogenesis testing of the freshly formed fumes produced by thermal conversion of nickel sulfide to nickel oxide. Efforts should be directed to identifying the chemical forms of nickel in tobacco smoke and their possible relation to respiratory carcinogenesis. Long-term evaluation of the safety of inhaled nickel-containing particles, using experimental animals, should be initiated as soon as possible. Investigations should be directed to elucidating the mechanisms of the acute hyperglycemia that is observed after administration of nickel salts.

5. *Metabolism of Nickel.* Further research is needed to clarify the

role of nickel in nutrition, with particular emphasis on its possible dietary essentiality; to elucidate the molecular binding sites for nickel that are physiologically significant or are involved in the detoxification and elimination of nickel compounds; and to determine the mechanisms and clinical importance of pathologic alterations of nickel concentrations in body fluids and tissues. Attention should be directed to the metabolism of nickel in diseases associated with intravascular thrombosis, such as myocardial infarction, stroke, and burns. Improvements are required in the sensitivity, precision, and accuracy of methods for nickel analysis in biologic materials.

6. *Dermatologic Investigations.* There are pressing needs for investigations into the prevalence, pathogenesis, prevention, and therapy of nickel dermatitis. Attempts should be made to develop a consistent animal model for the induction of skin sensitization to nickel. Studies should also be directed toward elucidating the allergic potential of nickel released from implanted therapeutic devices and prostheses, the role of the skin in the absorption and excretion of nickel, and the effects of nickel on enzymatic activities and metabolic processes in the skin.

Appendix A

National Air Surveillance Networks Ambient Nickel Concentrations

APPENDIX A: National Air Surveillance Networks[a] Ambient Nickel Concentrations

		Nickel Concentration, µg/m³				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
Alabama						
Birmingham	1965	0.006	0.011	0.000	0.000	0.004
	1966	0.014	0.022	0.014	0.014	0.016
Gadsden	1964	0.000	0.007	0.000	0.007	0.004
	1966	0.006	0.006	0.006	0.011	0.007
	1969	0.000	0.000	0.000	0.000	0.000
Huntsville	1965	0.006	0.000	0.000	0.000	0.002
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.009	0.009	0.000	0.000	0.005
Mobile	1964	0.025	0.008	0.005	0.054	0.023
	1966	0.013	0.012	0.014	0.014	0.013
	1969	0.017	0.010	0.014	0.000	0.010
Montgomery	1965	0.007	0.000	0.000	0.000	0.002
	1967	0.000	0.000	0.000	0.021	0.005
	1969	0.000	0.000	0.011	0.000	0.003
Alaska						
Anchorage-A	1966	0.000	0.023	0.020	0.026	0.017
-B	1967	0.000	0.007	0.020	0.013	0.010
-B	1969	0.000	0.009	0.011	0.011	0.008
Fairbanks*	1967	0.000	0.009	0.008	0.019	0.009
	1969	0.000	0.000	0.012	0.013	0.006
Arizona						
Grand Canyon*	1965	0.000	0.001	0.000	0.001	0.001
	1966	0.002	0.003	0.006	0.004	0.004
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Maricopa County*	1965	0.003	0.001	0.002	0.002	0.002
	1966	0.000	0.000	0.000	0.010	0.003
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Paradise Valley	1964	0.000	0.000	0.007	0.000	0.002
	1965	0.003	0.001	0.002	0.002	0.002
Phoenix	1965	0.017	0.012	0.010	0.006	0.011
	1966	0.014	0.019	0.010	0.011	0.014
	1967	0.014	0.010	0.013	0.009	0.012
	1969	0.011	0.000	0.000	0.009	0.003
Tucson	1964	0.000	0.007	0.000	0.000	0.002
	1965	0.006	0.009	0.000	0.000	0.004
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.010	0.000	0.000	0.003
Arkansas						
Little Rock	1964	0.008	0.000	0.000	0.000	0.002
	1966	0.000	0.000	0.012	0.000	0.003
	1	0.000	0.000	0.000	0.000	0.000
	1969	0.011	0.000	0.000	0.000	0.003

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Location[b]	Year	Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
		1st	4th	2nd	3rd	Year Avg.
Montgomery County*	1965	0.002	0.001	0.002	0.000	0.001
	1966	0.005	0.004	0.004	0.003	0.004
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Texarkana	1964	0.005	0.000	0.000	0.000	0.001
	1969	0.000	0.008	0.008	0.010	0.007
W. Memphis	1966	0.000	0.000	0.011	0.014	0.006
	1969	0.010	0.014	0.013	0.013	0.013
California						
Anaheim	1969	0.024	0.027	0.017	0.022	0.023
Bakersfield	1964	0.031	0.045	0.017	0.031	0.031
Burbank	1964	0.026	0.053	0.010	0.033	0.031
Fresno	1969	0.000	0.022	0.009	0.015	0.012
Glendale	1965	0.043	0.024	0.011	0.000	0.020
	1967	0.031	0.009	0.013	0.010	0.016
	1969	0.028	0.023	0.025	0.018	0.024
Humboldt County*	1965	0.002	0.000	0.001	0.002	0.001
	1966	0.006	0.004	0.004	0.005	0.005
	1967	0.000	0.003	0.000	0.000	0.001
	1969	0.000	0.000	0.000	0.000	0.000
Long Beach	1965	0.038	0.013	0.021	0.034	0.027
	1967	0.062	0.000	0.019	0.021	0.026
	1969	0.054	0.023	0.025	0.030	0.033
Los Angeles	1964	0.035	0.046	0.000	0.012	0.023
	1965	0.031	0.021	0.013	0.008	0.018
	1966	0.090	0.025	0.017	0.025	0.039
	1967	0.039	0.027	0.014	0.015	0.024
	1969	0.063	0.021	0.013	0.024	0.030
Monterey	1964	0.000	0.019	0.008	0.007	0.009
Oakland	1964	0.017	0.053	0.011	0.019	0.025
	1965	0.033	0.030	0.024	0.008	0.024
	1966	0.023	0.029	0.019	0.017	0.022
	1967	0.044	0.030	0.026	0.025	0.031
	1969	0.028	0.039	0.038	0.032	0.034
Ontario	1969	0.025	0.019	0.017	0.020	0.020
Pasadena	1964	0.037	0.025	0.009	0.011	0.021
	1966	0.055	0.014	0.013	0.019	0.025
Riverside	1969	0.029	0.015	0.020	0.020	0.021
Sacramento	1964	0.006	0.000	0.000	0.011	0.004
	1969	0.000	0.000	0.000	0.022	0.006
San Bernardino	1969	0.035	0.037	0.021	0.030	0.033
San Diego	1964	0.026	0.014	0.012	0.009	0.015
	1965	0.030	0.025	0.016	0.012	0.021
	1966	0.026	0.037	0.014	0.016	0.023
	1967	0.033	0.017	0.014	0.023	0.022
	1969	0.052	0.052	0.023	0.035	0.041
San Francisco	1965	0.023	0.030	0.007	0.008	0.017
	1966	0.042	0.057	0.006	0.011	0.029

		Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
	1967	0.045	0.027	0.000	0.000	0.018
	1969	0.028	0.050	0.018	0.017	0.028
San Jose	1963	0.019	0.006	0.013	0.011	0.012
	1969	0.018	0.019	0.013	0.015	0.016
Santa Ana	1964	0.032	0.039	0.005	0.009	0.021
	1969	0.022	0.027	0.016	0.021	0.022
Santa Barbara	1964	0.000	0.015	0.006	0.000	0.005
Torrance	1969	0.021	0.045	0.013	0.018	0.024
Colorado						
Denver	1965	0.000	0.012	0.000	0.011	0.006
	1966	0.011	0.007	0.000	0.006	0.006
	1969	0.011	0.073	0.015	0.020	0.030
Mesa Verde	1965	0.000	0.000	0.000	0.000	0.000
National Park*	1966	0.003	0.004	0.004	0.005	0.004
	1967	0.000	0.000	0.000	0.000	0.000
Montezuma County	1965	0.001	0.001	0.001	0.001	0.001
	1969	0.000	0.000	0.000	0.000	0.000
Connecticut						
Bridgeport	1962	0.042	0.038	0.022	0.019	0.030
	1969	0.041	0.100	0.041	0.035	0.054
Hartford	1964	0.053	0.049	0.019	0.015	0.034
	1965	0.020	0.086	0.023	0.025	0.039
	1966	0.047	0.068	0.026	0.015	0.039
	1969	0.083	0.060	0.053	0.032	0.057
New Britain	1965	0.029	0.040	0.027	0.017	0.028
New Haven	1964	0.038	0.043	0.044	0.021	0.037
	1966	0.120	0.058	0.110	0.029	0.079
	1967	0.160	0.110	0.080	0.020	0.093
	1969	0.230	0.200	0.088	0.042	0.140
Norwich	1965	0.035	0.027	0.028	0.023	0.028
Waterbury	1965	0.055	0.043	0.039	0.023	0.040
Delaware						
Kent County*	1966	0.019	0.018	0.006	0.009	0.013
	1967	0.008	0.008	0.005	0.004	0.006
Newark	1965	0.024	0.031	0.015	0.013	0.021
	1966	0.028	0.021	0.020	0.028	0.024
	1967	0.033	0.021	0.019	0.012	0.021
Wilmington-A	1964	0.150	0.100	0.074	0.039	0.091
-A	1965	0.043	0.046	0.031	0.035	0.039
-A	1966	0.047	0.052	0.037	0.014	0.038
-A	1967	0.056	0.044	0.038	0.023	0.040
-B	1969	0.150	0.120	0.043	0.060	0.093
District of Columbia						
	1965	0.027	0.025	0.012	0.049	0.028
	1966	0.025	0.021	0.011	0.012	0.017
	1967	0.032	0.043	0.018	0.020	0.028
	1969	0.070	0.039	0.040	0.022	0.043

Location[b]	Year	Nickel Concentration, μg/m³				
		Cold Quarters		Warm Quarters		
		1st	4th	2nd	3rd	Year Avg.
Florida						
Hardee County*	1969	0.000	0.000	0.000	0.000	0.000
Jacksonville	1969	0.048	0.014	0.077	0.025	0.041
Miami	1969	0.018	0.022	0.019	0.048	0.027
St. Petersburg	1969	0.021	0.010	0.009	0.013	0.013
Tampa	1969	0.016	0.012	0.015	0.021	0.016
Georgia						
Atlanta	1964	0.009	0.010	0.008	0.009	0.009
	1965	0.013	0.000	0.007	0.006	0.007
	1966	0.010	0.000	0.000	0.000	0.003
	1967	0.006	0.013	0.008	0.011	0.010
	1969	0.012	0.012	0.000	0.011	0.009
Columbus	1969	0.000	0.000	0.000	0.000	0.000
Savanah	1969	0.026	0.013	0.009	0.014	0.016
Hawaii						
Honolulu	1965	0.036	0.043	0.043	0.035	0.039
	1966	0.052	0.026	0.021	0.020	0.030
	1967	0.022	0.037	0.027	0.020	0.027
	1969	0.050	0.044	0.056	0.030	0.045
Idaho						
Boise City	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.000	0.010	0.003
	1969	0.000	0.000	0.000	0.020	0.005
Butte County*	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Illinois						
Chicago	1965	0.046	0.044	0.040	0.021	0.038
	1966	0.038	0.034	0.030	0.015	0.029
	1967	0.035	0.058	0.019	0.014	0.032
	1969	0.110	0.056	0.025	0.013	0.051
Joliet	1965	0.021	0.014	0.017	0.009	0.015
	1969	0.018	0.014	0.015	0.016	0.016
Moline	1964	0.005	0.007	0.008	0.007	0.007
North Chicago	1969	0.023	0.000	0.017	0.011	0.013
Peoria	1964	0.007	0.013	0.009	0.009	0.010
Rockford	1965	0.016	0.013	0.000	0.008	0.009
	1967	0.011	0.000	0.000	0.013	0.006
	1969	0.017	0.012	0.015	0.000	0.011
Rock Island	1964	0.007	0.007	0.017	0.017	0.012
Springfield	1965	0.006	0.000	0.000	0.008	0.004
	1967	0.000	0.000	0.000	0.009	0.002
	1969	0.012	0.000	0.000	0.017	0.007
Indiana						
Beverly Shores*	1965	0.005	0.000	0.000	0.010	0.004
East Chicago	1965	0.067	0.480	0.036	0.033	0.154
	1966	0.031	0.046	0.048	0.019	0.036

		Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
	1967	0.050	0.037	0.030	0.025	0.036
	1969	0.110	0.084	0.170	0.052	0.104
Evansville	1964	0.007	0.000	0.000	0.000	0.002
	1969	0.016	0.010	0.011	0.013	0.013
Fort Wayne	1964	0.000	0.014	0.000	0.000	0.004
	1969	0.013	0.017	0.015	0.012	0.014
Gary	1969	0.025	0.020	0.009	0.017	0.018
Hammond	1965	0.027	0.022	0.024	0.018	0.023
	1966	0.012	0.010	0.022	0.013	0.014
	1967	0.022	0.028	0.035	0.021	0.027
	1969	0.039	0.030	0.027	0.021	0.029
Indianapolis	1965	0.018	0.021	0.017	0.018	0.019
	1966	0.016	0.024	0.011	0.023	0.019
	1967	0.015	0.017	0.024	0.019	0.019
	1969	0.027	0.021	0.025	0.019	0.023
Monroe County*	1966	0.004	0.004	0.003	0.002	0.003
	1967	0.000	0.002	0.000	0.002	0.001
	1969	0.000	0.000	0.000	0.016	0.004
New Albany	1966	0.015	0.025	0.009	0.011	0.015
	1969	0.016	0.013	0.013	0.020	0.018
Parke County*	1965	0.003	0.002	0.004	0.003	0.003
	1966	0.008	0.008	0.004	0.003	0.006
	1967	0.002	0.003	0.003	0.006	0.004
	1969	0.000	0.000	0.000	0.000	0.000
Porter County*-A	1965	0.005	0.000	0.000	0.010	0.004
-B	1965	0.013	0.011	0.000	0.010	0.009
-C	1965	0.013	0.013	0.009	0.014	0.012
-D	1965	0.006	0.014	0.000	0.000	0.005
South Bend	1965	0.083	0.064	0.011	0.000	0.040
	1966	0.041	0.015	0.000	0.010	0.017
	1967	0.024	0.000	0.006	0.006	0.009
	1969	0.016	0.018	0.038	0.011	0.021
Terre Haute	1963	0.009	0.007	0.000	0.000	0.004
	1967	0.007	0.000	0.008	0.010	0.006
	1969	0.011	0.000	0.011	0.000	0.006
West Lafayette	1964	0.008	0.022	0.008	0.005	0.011
Iowa						
Cedar Rapids	1965	0.011	0.008	0.012	0.000	0.008
	1967	0.007	0.000	0.011	0.000	0.005
Davenport	1966	0.006	0.000	0.000	0.018	0.006
	1969	0.022	0.013	0.014	0.013	0.016
Delaware County*	1965	0.001	0.001	0.001	0.002	0.001
Des Moines	1965	0.010	0.000	0.008	0.012	0.008
	1966	0.009	0.000	0.000	0.010	0.005
	1967	0.007	0.000	0.009	0.010	0.007
	1969	0.010	0.000	0.010	0.009	0.007

		Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
Dubuque	1964	0.000	0.010	0.000	0.000	0.003
	1966	0.000	0.009	0.006	0.009	0.006
	1967	0.007	0.000	0.008	0.012	0.007
	1969	0.018	0.012	0.010	0.000	0.010
Kansas						
Kansas City	1964	0.011	0.022	0.000	0.006	0.010
	1966	0.000	0.000	0.000	0.000	0.000
	1969	0.016	0.018	0.010	0.012	0.014
Topeka	1965	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Wichita	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.008	0.000	0.000	0.000	0.002
Kentucky						
Ashland	1964	0.016	0.025	0.038	0.007	0.022
	1966	0.011	0.019	0.016	0.022	0.017
	1969	0.280	0.059	0.021	0.091	0.113
Covington	1964	0.007	0.007	0.007	0.012	0.008
	1966	0.017	0.010	0.006	0.012	0.011
	1967	0.000	0.000	0.000	0.008	0.002
	1969	0.011	0.012	0.012	0.019	0.014
Lexington	1965	0.000	0.000	0.000	0.000	0.000
	1967	0.007	0.000	0.006	0.009	0.006
Louisville	1964	0.032	0.058	0.029	0.021	0.035
	1965	0.026	0.031	0.030	0.075	0.041
	1966	0.016	0.046	0.044	0.018	0.031
	1967	0.042	0.010	0.036	0.029	0.029
	1969	0.024	0.025	0.041	0.028	0.030
Louisiana						
Baton Rouge	1964	0.000	0.006	0.000	0.000	0.002
	1969	0.000	0.008	0.000	0.000	0.002
Lake Charles	1964	0.000	0.000	0.000	0.000	0.000
New Orleans	1964	0.020	0.012	0.019	0.010	0.016
	1965	0.024	0.023	0.012	0.007	0.017
	1966	0.013	0.012	0.000	0.006	0.008
	1969	0.180	0.038	0.054	0.023	0.074
Shreveport	1965	0.009	0.011	0.011	0.011	0.011
	1969	0.008	0.008	0.000	0.000	0.004
Maine						
Acadia National Park*	1965	0.002	0.013	0.017	0.014	0.011
	1966	0.009	0.006	0.007	0.007	0.007
	1967	0.033	0.025	0.016	0.014	0.022
	1969	0.013	0.005	0.025	0.008	0.013
Maryland						
Baltimore	1965	0.045	0.040	0.020	0.030	0.034
	1966	0.066	0.130	0.048	0.039	0.071

		Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
	1967	0.062	0.042	0.036	0.031	0.043
	1969	0.110	0.074	0.072	0.046	0.076
Calvert County*	1965	0.003	0.004	0.002	0.003	0.003
	1966	0.009	0.007	0.006	0.004	0.007
	1967	0.022	0.007	0.012	0.012	0.013
	1969	0.009	0.005	0.036	0.018	0.017
Massachusetts						
Boston	1969	0.140	0.130	0.072	0.046	0.097
Brockton	1965	0.011	0.024	0.014	0.015	0.016
Fall River	1969	0.091	0.054	0.040	0.030	0.054
Lynn	1962	0.047	—	0.048	0.024	0.030
Somerville	1962	0.063	0.068	0.046	0.032	0.052
Springfield	1964	0.024	0.027	0.016	0.013	0.020
	1969	0.061	0.059	0.026	0.027	0.043
Worcester	1969	0.044	0.100	0.036	0.026	0.052
Michigan						
Dearborn	1969	0.016	0.015	0.015	0.014	0.015
Detroit	1965	0.026	0.017	0.014	0.019	0.019
	1966	0.014	0.021	0.046	0.016	0.024
	1967	0.016	0.043	0.020	0.028	0.027
	1969	0.025	0.020	0.034	0.023	0.026
Flint	1965	0.051	0.011	0.011	0.007	0.020
	1967	0.000	0.000	0.007	0.006	0.003
	1969	0.013	0.010	0.019	0.000	0.011
Grand Rapids	1965	0.000	0.016	0.013	0.017	0.012
	1967	0.009	0.006	0.006	0.013	0.009
	1969	0.014	0.009	0.019	0.009	0.013
Kalamazoo	1960	0.008	0.018	0.014	0.005	0.011
Lansing	1969	0.000	0.000	0.010	0.000	0.003
Muskegon	1963	0.011	0.008	0.011	0.011	0.010
Saginaw	1969	0.000	0.000	0.009	0.000	0.002
Trenton	1965	0.012	0.009	0.000	0.014	0.009
	1969	0.016	0.012	0.017	0.009	0.014
Minnesota						
Duluth	1964	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.014	0.010	0.006
Minneapolis	1965	0.010	0.000	0.008	0.006	0.006
	1966	0.013	0.007	0.000	0.000	0.005
	1967	0.012	0.000	0.000	0.011	0.006
	1969	0.017	0.012	0.011	0.000	0.010
Moorhead	1964	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.000	0.000
St. Paul	1964	0.011	0.012	0.008	0.000	0.008
	1966	0.014	0.000	0.000	0.000	0.004
	1967	0.025	0.011	0.000	0.000	0.009
	1969	0.035	0.004	0.000	0.000	0.011

Location[b]	Year	Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
		1st	4th	2nd	3rd	Year Avg.
Mississippi						
Jackson	1965	0.000	0.006	0.000	0.000	0.002
	1966	0.000	0.000	0.000	0.000	0.000
Jackson County*	1965	0.012	0.012	0.014	0.013	0.013
	1966	0.012	0.003	0.014	0.007	0.009
	1967	0.006	0.002	0.000	0.009	0.004
Missouri						
Kansas City	1964	0.021	0.012	0.005	0.006	0.011
	1965	0.018	0.021	0.011	0.010	0.015
	1966	0.006	0.009	0.000	0.000	0.004
	1967	0.011	0.000	0.012	0.010	0.008
	1969	0.016	0.011	0.009	0.000	0.009
St. Louis	1965	0.014	0.015	0.013	0.014	0.014
	1966	0.016	0.007	0.006	0.016	0.011
	1967	0.014	0.007	0.012	0.006	0.010
	1969	0.019	0.032	0.016	0.015	0.021
Shannon County*-A	1965	0.001	0.001	0.002	0.003	0.002
-A	1966	0.000	0.002	0.000	0.003	0.001
-A	1967	0.000	0.000	0.000	0.000	0.000
-B	1969	0.000	0.000	0.000	0.000	0.000
Montana						
Glacier National Park*	1965	0.002	0.000	0.010	0.002	0.003
	1966	0.000	0.000	0.002	0.003	0.001
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Helena	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Nebraska						
Lincoln	1962	0.008	0.000	0.005	0.008	0.005
Omaha	1965	0.010	0.000	0.009	0.000	0.005
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.008	0.011	0.005
	1969	0.000	0.000	0.010	0.009	0.005
Thomas County*	1965	0.002	0.000	0.002	0.001	0.001
	1966	0.000	0.000	0.000	0.002	0.001
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Nevada						
Las Vegas	1965	0.000	0.000	0.000	0.006	0.002
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.010	0.000	0.010	0.005
Reno	1965	0.059	0.075	0.030	0.025	0.047
	1967	0.087	0.025	0.025	0.040	0.044
	1969	0.089	0.074	0.041	0.043	0.060

Location^b	Year	Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
		1st	4th	2nd	3rd	Year Avg.
White Pine County*	1965	0.002	0.000	0.001	0.000	0.001
	1966	0.000	0.000	0.003	0.002	0.001
	1967	0.002	0.000	0.000	0.002	0.001
	1969	0.000	0.000	0.000	0.000	0.000
New Hampshire						
Concord	1964	0.013	0.010	0.009	0.013	0.011
	1965	0.007	0.010	0.000	0.006	0.006
	1966	0.012	0.015	0.006	0.014	0.012
	1967	0.027	0.018	0.014	0.014	0.018
	1969	0.013	0.023	0.021	0.011	0.017
Coos County*	1965	0.001	0.003	0.002	0.003	0.002
	1966	0.004	0.008	0.006	0.008	0.007
	1967	0.005	0.003	0.000	0.003	0.003
	1969	0.000	0.000	0.000	0.000	0.000
New Jersey						
Bayonne	1967	0.130	0.082	0.033	0.052	0.074
Bridgeton	1965	0.013	0.009	0.009	0.013	0.011
Burlington						
County*-A	1965	0.016	0.027	0.010	0.010	0.016
-B	1965	0.023	0.035	0.017	0.021	0.024
-B	1966	0.025	0.061	0.076	0.016	0.045
-B	1967	0.040	0.011	0.022	0.023	0.024
-B	1969	0.029	0.023	0.020	0.021	0.023
Camden	1964	0.170	0.083	0.049	0.060	0.091
	1966	0.054	0.030	0.017	0.033	0.034
Elizabeth	1969	0.056	0.044	0.036	0.041	0.044
Glassboro*	1964	0.019	0.021	0.012	0.010	0.016
	1965	0.023	0.012	0.014	0.016	0.016
	1966	0.015	0.012	0.006	0.013	0.012
	1967	0.013	0.000	0.014	0.017	0.011
	1969	0.027	0.021	0.022	0.031	0.025
Hamilton	1965	0.039	0.091	0.056	0.021	0.052
	1969	0.034	0.043	0.018	0.029	0.031
Jersey City	1965	0.091	0.100	0.030	0.057	0.07[illegible]
	1966	0.073	0.064	0.022	0.051	0.05[illegible]
	1967	0.076	0.038	0.150	0.037	0.075
	1969	0.084	0.062	0.064	0.049	0.065
Newark	1965	0.100	0.081	0.064	0.048	0.073
	1966	0.071	0.041	0.024	0.064	0.050
	1967	0.140	0.031	0.073	0.068	0.078
	1969	0.071	0.068	0.034	0.051	0.056
Paterson	1965	0.180	0.084	0.066	0.081	0.103
	1967	0.100	0.034	0.160	0.027	0.080
	1969	0.069	0.120	0.037	0.040	0.067
Perth Amboy	1965	0.077	0.053	0.040	0.067	0.059
	1966	0.035	0.040	0.025	0.076	0.044
	1967	0.120	0.020	0.065	0.068	0.068
	1969	0.073	0.043	0.028	0.035	0.045

		Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
Trenton	1966	0.025	0.039	0.027	0.020	0.028
	1969	0.051	0.034	0.064	0.041	0.048
New Mexico						
Albuquerque	1964	0.000	0.000	0.000	0.000	0.000
	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.008	0.000	0.000	0.000	0.002
	1967	0.011	0.000	0.000	0.007	0.005
	1969	0.000	0.000	0.000	0.000	0.000
Rio Arriba County*	1965	0.002	0.002	0.003	0.002	0.002
	1966	0.004	0.003	0.005	0.004	0.004
	1967	0.000	0.000	0.003	0.000	0.001
New York						
Albany	1969	0.049	0.040	0.024	0.029	0.036
Buffalo	1969	0.033	0.036	0.027	0.024	0.030
Cape Vincent*	1965	0.003	0.006	0.003	0.002	0.003
Jefferson County*	1965	0.003	0.006	0.003	0.002	0.004
	1966	0.006	0.004	0.004	0.007	0.005
	1967	0.004	0.005	0.005	0.004	0.005
	1969	0.014	0.008	0.007	0.007	0.009
New York City	1965	0.290	0.200	0.025	0.110	0.156
	1966	0.089	0.060	0.042	0.041	0.058
	1967	0.200	0.070	0.240	0.240	0.188
	1969	0.330	0.130	0.180	0.052	0.173
Niagara Falls	1969	0.021	0.012	0.042	0.033	0.027
Rochester	1969	0.024	0.023	0.012	0.021	0.020
Syracuse	1969	0.037	0.022	0.014	0.013	0.022
Utica	1969	0.028	0.029	0.018	0.015	0.023
North Carolina						
Cape Hatteras*	1965	0.003	0.005	0.000	0.002	0.003
	1966	0.004	0.015	0.003	0.002	0.006
	1967	0.004	0.003	0.002	0.002	0.003
	1969	0.007	0.039	0.005	0.091	0.036
Charlotte	1965	0.013	0.007	0.009	0.007	0.009
	1966	0.000	0.016	0.009	0.010	0.009
	1967	0.007	0.000	0.000	0.014	0.005
	1969	0.022	0.013	0.000	0.010	0.011
Durham	1969	0.008	0.008	0.000	0.000	0.004
Fayetteville	1964	0.000	0.000	0.000	0.000	0.000
Greensboro	1969	0.013	0.014	0.009	0.008	0.011
Winston-Salem	1969	0.013	0.014	0.000	0.000	0.007
North Dakota						
Bismarck	1969	0.000	0.000	0.000	0.000	0.000
Ohio						
Akron	1964	0.007	0.023	0.021	0.020	0.018
	1965	0.014	0.019	0.013	0.023	0.017
	1966	0.006	0.018	0.011	0.013	0.012
	1967	0.016	0.000	0.014	0.020	0.013
	1969	0.012	0.011	0.012	0.015	0.013

Location[b]	Year	Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
		1st	4th	2nd	3rd	Year Avg.
Canton	1969	0.025	0.017	0.050	0.050	0.036
Cincinnati	1965	0.020	0.015	0.010	0.012	0.014
	1966	0.008	0.012	0.016	0.014	0.013
	1967	0.021	0.008	0.009	0.021	0.015
	1969	0.019	0.018	0.018	0.022	0.019
Cleveland	1965	0.019	0.017	0.022	0.011	0.017
	1966	0.011	0.006	0.012	0.013	0.011
	1967	0.020	0.006	0.021	0.011	0.015
	1969	0.017	0.013	0.031	0.022	0.021
Columbus	1964	0.023	0.020	0.024	0.009	0.019
	1965	0.026	0.030	0.017	0.028	0.025
	1966	0.010	0.023	0.015	0.020	0.017
	1967	0.016	0.008	0.023	0.013	0.015
	1969	0.024	0.019	0.047	0.033	0.031
Dayton	1964	0.000	0.021	0.014	0.000	0.009
	1966	0.010	0.009	0.012	0.000	0.008
	1967	0.015	0.015	0.013	0.015	0.015
	1969	0.012	0.009	0.014	0.009	0.011
Steubenville	1964	0.018	0.035	0.024	0.025	0.026
Toledo	1965	0.017	0.010	0.012	0.009	0.012
	1966	0.006	0.006	0.015	0.007	0.009
	1967	0.012	0.006	0.010	0.024	0.013
	1969	0.010	0.008	0.013	0.000	0.008
Youngstown	1964	0.023	0.010	0.020	0.015	0.017
	1965	0.020	0.016	0.015	0.017	0.017
	1966	0.017	0.018	0.025	0.045	0.026
	1967	0.023	0.011	0.023	0.021	0.020
	1969	0.100	0.022	0.034	0.026	0.040
Oklahoma						
Cherokee County*	1965	0.001	0.001	0.001	0.002	0.001
	1966	0.004	0.005	0.003	0.004	0.004
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Oklahoma City	1964	0.000	0.000	0.000	0.000	0.000
	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.006	0.000	0.002
	1969	0.000	0.000	0.000	0.000	0.000
Tulsa	1964	0.000	0.000	0.000	0.000	0.000
	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.000	0.008	0.002
	1969	0.009	0.011	0.000	0.000	0.005
Oregon						
Curry County*	1965	0.003	0.001	0.001	0.002	0.002
	1966	0.006	0.003	0.002	0.003	0.004
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.005	0.000	0.000	0.001

		Nickel Concentration, µg/m³				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
Eugene	1965	0.010	0.007	0.011	0.006	0.009
	1967	0.011	0.000	0.011	0.020	0.011
Medford	1965	0.013	0.022	0.013	0.018	0.017
	1967	0.008	0.000	0.007	0.016	0.008
	1969	0.016	0.033	0.011	0.009	0.017
Portland	1965	0.094	0.060	0.045	0.038	0.059
	1966	0.041	0.049	0.031	0.031	0.038
	1967	0.028	0.027	0.070	0.041	0.042
	1969	0.065	0.110	0.071	0.037	0.071
Pennsylvania						
Allentown	1967	0.031	0.006	0.033	0.018	0.022
	1969	0.041	0.071	0.031	0.027	0.043
Altoona	1965	0.011	0.000	0.000	0.008	0.005
	1967	0.011	0.000	0.013	0.012	0.009
Bethlehem-A	1965	0.019	0.033	0.010	0.012	0.019
-A	1967	0.035	0.007	0.030	0.018	0.023
-B	1969	0.030	0.037	0.026	0.026	0.030
Bucks County*	1965	0.009	0.014	0.013	0.011	0.012
Chester County*	1965	0.022	0.015	0.021	0.014	0.018
Clarion County*	1965	0.004	0.004	0.004	0.003	0.004
	1966	0.005	0.005	0.003	0.005	0.005
	1967	0.006	0.007	0.005	0.005	0.006
	1969	0.008	0.006	0.005	0.000	0.005
Erie	1965	0.023	0.007	0.013	0.012	0.014
	1969	0.000	0.000	0.014	0.048	0.016
Harrisburg	1969	0.025	0.022	0.034	0.028	0.027
Hazleton	1969	0.012	0.000	0.000	0.000	0.003
Johnstown	1965	0.040	0.030	0.028	0.025	0.031
	1969	0.012	0.000	0.019	0.013	0.011
Lancaster City	1965	0.013	0.019	0.016	0.020	0.017
	1966	0.015	0.020	0.009	0.019	0.016
	1967	0.033	0.009	0.015	0.007	0.016
Philadelphia	1965	0.190	0.200	0.082	0.020	0.123
	1966	0.052	0.040	0.025	0.030	0.037
	1967	0.110	0.031	0.084	0.026	0.063
	1969	0.110	0.110	0.067	0.098	0.096
Pittsburgh	1965	0.024	0.011	0.020	0.039	0.024
	1966	0.019	0.020	0.019	0.032	0.023
	1967	0.026	0.019	0.031	0.035	0.028
	1969	0.026	0.020	0.053	0.071	0.043
Reading	1965	0.043	0.110	0.032	0.063	0.062
	1966	0.068	0.031	0.033	0.024	0.039
	1967	0.093	0.024	0.020	0.017	0.039
	1969	0.097	0.095	0.110	0.190	0.123
Scranton	1965	0.028	0.022	0.027	0.019	0.024
Warminster*	1965	0.016	0.017	0.025	0.017	0.019
	1966	0.055	0.011	0.013	0.011	0.023

		Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
Location^b	Year	1st	4th	2nd	3rd	Year Avg.
	1967	0.035	0.016	0.018	0.012	0.020
	1969	0.020	0.022	0.016	0.017	0.019
West Chester	1965	0.015	0.015	0.011	0.010	0.013
	1967	0.018	0.010	0.018	0.000	0.012
	1969	0.015	0.018	0.013	0.023	0.017
Wilkes-Barre	1969	0.016	0.014	0.015	0.009	0.014
York	1965	0.036	0.024	0.024	0.015	0.025
	1967	0.031	0.019	0.018	0.013	0.020
	1969	0.035	0.042	0.026	0.019	0.031
Puerto Rico						
Bayamon	1965	0.024	0.013	0.033	0.012	0.021
	1966	0.017	0.008	0.016	0.015	0.014
	1967	0.033	0.074	0.014	0.015	0.034
	1969	0.038	0.028	0.014	0.009	0.022
Catano-A	1965	0.048	0.050	0.048	0.041	0.047
-A	1966	0.027	0.031	0.020	0.060	0.035
-A	1967	0.013	0.007	0.035	0.031	0.022
-B	1969	0.093	0.034	0.089	0.120	0.084
Guayanilla*	1966	0.000	0.008	0.000	0.008	0.004
	1967	0.000	0.000	0.018	0.014	0.008
	1969	0.029	0.054	0.049	0.042	0.044
Ponce	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.008	0.000	0.000	0.007	0.004
	1969	0.009	0.017	0.000	0.014	0.010
San Juan	1969	0.000	0.016	0.020	0.018	0.014
Rhode Island						
East Providence	1965	0.021	0.059	0.021	0.020	0.030
	1967	0.029	0.012	0.019	0.016	0.019
	1969	0.057	0.045	0.040	0.027	0.042
Providence	1965	0.110	0.006	0.030	0.022	0.042
	1966	0.120	0.043	0.058	0.014	0.059
	1967	0.053	0.034	0.046	0.017	0.038
	1969	0.210	0.170	0.043	0.027	0.113
Washington County*-A	1965	0.005	0.013	0.011	0.004	0.008
-A	1966	0.014	0.007	0.008	0.006	0.009
-A	1967	0.013	0.006	0.011	0.009	0.010
-B	1969	0.017	0.010	0.010	0.009	0.012
South Carolina						
Charleston	1965	0.006	0.015	0.000	0.000	0.005
Columbia	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.008	0.000	0.000	0.000	0.002
Greenville	1966	0.012	0.000	0.000	0.000	0.003
	1969	0.010	0.010	0.012	0.000	0.008
Richland County*	1965	0.003	0.002	0.001	0.000	0.001
	1966	0.003	0.003	0.003	0.000	0.002
	1967	0.006	0.010	0.004	0.000	0.005
	1969	0.000	0.000	0.000	0.000	0.000

Location[b]	Year	Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
		1st	4th	2nd	3rd	Year Avg.
Spartanburg	1965	0.009	0.011	0.000	0.006	0.007
South Dakota						
Black Hills National Forest*	1965	0.000	0.001	0.002	0.000	0.001
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.005	0.000	0.000	0.001
	1969	0.000	0.000	0.000	0.000	0.000
Sioux Falls	1966	0.000	0.000	0.000	0.000	0.000
Tennessee						
Chattanooga	1965	0.020	0.023	0.011	0.000	0.014
	1966	0.013	0.017	0.009	0.007	0.012
	1967	0.017	0.018	0.000	0.009	0.011
	1969	0.020	0.013	0.015	0.015	0.016
Cumberland County*	1969	0.006	0.000	0.000	0.000	0.002
Knoxville	1965	0.006	0.012	0.007	0.000	0.006
	1967	0.006	0.000	0.006	0.000	0.003
	1969	0.011	0.010	0.008	0.009	0.010
Memphis	1965	0.000	0.000	0.006	0.000	0.002
	1966	0.000	0.008	0.000	0.000	0.002
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.009	0.000	0.008	0.004
Nashville	1965	0.008	0.009	0.000	0.007	0.006
	1966	0.007	0.007	0.006	0.006	0.007
	1967	0.007	0.000	0.013	0.000	0.005
	1969	0.011	0.010	0.014	0.000	0.009
Texas						
Dallas-A	1965	0.010	0.000	0.009	0.010	0.007
-A	1966	0.000	0.000	0.008	0.000	0.002
-B	1969	0.010	0.009	0.008	0.009	0.009
El Paso	1969	0.010	0.012	0.016	0.011	0.012
Fort Worth	1969	0.000	0.000	0.000	0.000	0.000
Houston	1966	0.011	0.009	0.000	0.011	0.008
	1967	0.012	0.000	0.000	0.010	0.006
	1969	0.021	0.024	0.019	0.025	0.022
Matagorda County*	1965	0.003	0.001	0.001	0.002	0.002
	1966	0.003	0.000	0.004	0.000	0.002
	1967	0.002	0.000	0.000	0.000	0.001
	1969	0.000	0.000	0.000	0.000	0.000
Pasadena	1967	0.000	0.000	0.033	0.006	0.010
	1969	0.028	0.018	0.019	0.020	0.021
San Antonio	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.009	0.000	0.002
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Texarkana	1964	0.000	0.000	0.000	0.000	0.000
Waco	1964	0.000	0.007	0.000	0.000	0.002
Utah						
Ogden	1966	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.013	0.011	0.006

		Nickel Concentration, μg/m³				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
Salt Lake City	1965	0.026	0.012	0.000	0.009	0.012
	1966	0.000	0.000	0.000	0.006	0.002
	1967	0.010	0.000	0.007	0.000	0.004
	1969	0.011	0.016	0.000	0.000	0.007
Vermont						
Burlington	1965	0.015	0.015	0.012	0.014	0.014
	1966	0.017	0.031	0.030	0.032	0.028
	1969	0.021	0.026	0.037	0.015	0.025
Orange County*	1965	0.008	0.007	0.000	0.003	0.005
	1966	0.008	0.007	0.008	0.005	0.007
	1967	0.012	0.011	0.010	0.004	0.009
	1969	0.011	0.017	0.007	0.011	0.012
Virginia						
Danville	1966	0.013	0.000	0.000	0.008	0.005
	1969	0.011	0.010	0.000	0.011	0.008
Hampton	1965	0.009	0.008	0.008	0.011	0.009
	1967	0.012	0.000	0.013	0.006	0.008
	1969	0.012	0.012	0.010	0.012	0.012
Lynchburg	1965	0.024	0.010	0.008	0.011	0.013
	1967	0.007	0.000	0.006	0.000	0.003
	1969	0.013	0.000	0.000	0.009	0.006
Newport News	1969	0.015	0.020	0.017	0.011	0.016
Norfolk	1965	0.025	0.019	0.018	0.017	0.020
	1966	0.007	0.015	0.007	0.013	0.011
	1967	0.019	0.012	0.012	0.018	0.015
	1969	0.037	0.028	0.026	0.021	0.028
Portsmouth	1965	0.022	0.014	0.021	0.017	0.019
	1967	0.012	0.000	0.018	0.009	0.010
	1969	0.032	0.023	0.018	0.022	0.024
Richmond	1965	0.023	0.028	0.025	0.010	0.022
	1967	0.019	0.012	0.012	0.007	0.013
	1969	0.029	0.024	0.018	0.013	0.021
Roanoke	1965	0.013	0.014	0.008	0.015	0.013
	1967	0.007	0.000	0.000	0.007	0.004
	1969	0.010	0.014	0.013	0.009	0.012
Shenandoah National Park*	1965	0.003	0.002	0.003	0.002	0.002
	1966	0.003	0.003	0.003	0.004	0.003
	1967	0.000	0.003	0.000	0.000	0.001
	1969	0.007	0.005	0.004	0.000	0.004
Wythe County	1969	0.004	0.000	0.000	0.000	0.001
Washington						
Seattle	1964	0.051	0.057	0.043	0.021	0.043
	1965	0.059	0.046	0.024	0.030	0.040
	1966	0.039	0.061	0.026	0.020	0.037
	1967	0.043	0.030	0.023	0.014	0.028
	1969	0.065	0.077	0.035	0.023	0.050
Spokane	1969	0.012	0.017	0.000	0.012	0.010
Tacoma	1969	0.068	0.065	0.041	0.024	0.050

		Nickel Concentration, $\mu g/m^3$				
		Cold Quarters		Warm Quarters		
Location[b]	Year	1st	4th	2nd	3rd	Year Avg.
West Virginia						
Charleston	1965	0.016	0.023	0.012	0.013	0.016
	1966	0.019	0.010	0.010	0.013	0.013
	1967	0.012	0.007	0.017	0.013	0.012
	1969	0.018	0.011	0.036	0.022	0.022
Huntington	1964	0.140	0.340	0.320	0.091	0.223
Wisconsin						
Door County*	1965	0.001	0.002	0.002	0.002	0.002
	1967	0.004	0.000	0.004	0.000	0.002
	1969	0.000	0.000	0.000	0.000	0.000
Eau Claire	1969	0.009	0.000	0.000	0.000	0.002
Kenosha	1965	0.007	0.012	0.011	0.006	0.009
	1967	0.009	0.000	0.000	0.000	0.002
	1969	0.011	0.018	0.015	0.008	0.013
Madison	1965	0.010	0.000	0.006	0.000	0.004
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.009	0.000	0.000	0.000	0.002
Milwaukee	1965	0.013	0.014	0.019	0.010	0.014
	1966	0.007	0.009	0.000	0.018	0.009
	1967	0.007	0.009	0.019	0.008	0.011
	1969	0.008	0.011	0.014	0.014	0.012
Racine	1969	0.000	0.008	0.000	0.000	0.002
Superior	1964	0.009	0.000	0.000	0.000	0.002
	1969	0.011	0.009	0.000	0.000	0.005
Wyoming						
Casper	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Cheyenne	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.000	0.000
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000
Yellowstone National Park*	1965	0.000	0.000	0.000	0.000	0.000
	1966	0.000	0.000	0.000	0.003	0.001
	1967	0.000	0.000	0.000	0.000	0.000
	1969	0.000	0.000	0.000	0.000	0.000

		Urban Stations Totals (542 samples/quarter)		
Cold Quarters		Warm Quarters		
1st	4th	2nd	3rd	Year
14.827	12.478	10.009	8.893	46.207
0.025 (average)		0.017 (average)		0.021 (average)
		Nonurban Stations Totals (151 samples/quarter)		
Cold Quarters		Warm Quarters		
1st	4th	2nd	3rd	Year
0.988	0.922	0.859	0.887	3.656
0.006 (average)		0.006 (average)		0.006 (average)

[a] Until 1967, called National Air Sampling Network.

[b] Asterisks indicate nonurban stations; all others are urban.

Appendix B

Analytic Methods for Nickel

NICKEL IN AIR

Air Sampling and Chemical Treatment of Samples

Air pollutants containing nickel are usually in the form of particles; samples can be collected with high-volume filters, sequential tape filters, electrostatic precipitators, scrubbers, and impingers. The National Air Sampling Network (NASN) has used a high-volume filtration sampler[659] to sample air for nickel.

Particulate samples of nickel collected on paper or fiberglass filters and on impingers can be treated with a small volume of nitric acid and heated. The nickel is thus brought into solution. The solution may be boiled to remove the excess of nitrogen oxides, cooled, and made up to a known volume in a volumetric flask. Nickel in the solution can be determined by such methods as atomic-absorption spectrometry and spectrophotometry.

Atomic-Absorption Spectrometry

Atomic-absorption spectrometry has been accepted as one of the most nearly ideal analytic techniques. Its combination of inherently high specificity and simplicity makes it widely applicable for air or water pollution studies. A method using an atomic-absorption spectrometer is therefore recommended for the determination of nickel in air. Some details of a typical system are listed in Table B-1.

Standard nickel solutions are prepared in the range of 2–25 μg/ml, preferably in the same media as sample solutions are likely to be in. These standard solutions are aspirated into the flame of the atomic-absorption spectrometer after the instrument has been adjusted according to proper operating conditions (Table B-1), and the absorbance is measured. A calibration curve is constructed by plotting absorbance against nickel concentrations. This procedure has a nickel sensitivity of 0.15 μg/ml.[10] However, using a heated graphite tube[366] for atomizing the samples increases the sensitivity to 0.015 μg/ml.

An excellent solvent-extraction method reported by Sachdev and West[508] is simple, rapid, and sensitive for nickel. A mixed-ligand system containing 0.1% dithizone, 0.75% 8-quinolinol, and 20% acetylacetone in ethylpropionate is used. The appropriate volume of the aqueous solution is conditioned with 10 ml of 1 *M* ammonium tartrate per 100 ml of sample solution. The pH of the solution should be adjusted to 6 ± 0.5 with ammonium hydroxide or tartaric acid; the solution is transferred to a 250-ml separatory funnel. Nickel is extracted into the organic phase by adding 10 ml of ligand mixture and shaking the two phases briskly for 1 min. The two layers are allowed to separate; the organic extract is collected carefully into a glass-stoppered bottle, and nickel is determined by aspirating the extract into the air–acetylene flame of an atomic-absorption spectrometer. The method is free from interferences, and nickel concentrations as low as 0.004 ppm can be determined.

As modified by Dharamarajan and West (unpublished data), the above method is well suited for air samples collected on membrane or fiberglass filters. A portion of a filter holding the sample (about 2 in. in diameter) is placed in a Petri dish and moistened with 2 ml of 15% am-

TABLE B-1 Characteristics of Atomic-Absorption Spectrometer for Determination of Nickel (303 Perkin-Elmer Instrument)

Wavelength	232 nm
Slit	3.0
Source	Perkin-Elmer hollow cathode
Lamp current	As recommended by the manufacturer
Acetylene	Flow 9.00
Air	Flow 9.00
Nickel sensitivity	0.15 μg/ml for 1% absorption; detection limit, 0.01 μg/ml
Range of nickel determination	2–25 μg/ml

monium acetate solution. Ten milliliters of ligand mixture are added, and the Petri dish is shaken slowly for 1 min to allow nickel particles to dissolve and transfer into the organic phase. The final nickel determination is carried out by aspirating the extract into the flame of an atomic-absorption spectrometer. The method is simple, quick, sensitive down to 0.0005 $\mu g/m^3$ of air (based on the sampling of 2,000 m^3 of air), and free of interferences.

In spite of the general advantages of atomic-absorption spectrometry for the determination of most metals, there is a complication with regard to nickel. The air–acetylene flame absorbs at the wavelength used for measuring nickel (232 nm), and this absorption increases if organic solvents, such as ethylpropionate or methylisobutylketone, are aspirated into the flame. To preclude errors due to flame background, it is usually recommended that the flame background absorbance be adjusted to a zero signal while only the solvent is being aspirated. In practice, this technique leaves much to be desired, and the use of a deuterium-arc background corrector (available from Perkin-Elmer) is recommended.

Spectrophotometry

A spectrophotometric method for the determination of nickel using dimethylglyoxime has been known for several decades. Many elegant spectrophotometric methods are available[516] that incorporate the use of various organic analytic reagents, but none exceeds the simplicity, specificity, and sensitivity of the dimethylglyoxime method.

To 5–25 ml of sample solution (preferably containing more than 5 μg and less than 100 μg of nickel) 5 ml of 10% citric acid is added. The solution is neutralized with concentrated ammonia, with a few drops in excess (pH <7.5) added. For each 10 mg, 2 ml of 1% ethanolic dimethylglyoxime and 5 ml of cobalt are added. Nickel is extracted from the solution three times with 3-ml portions of chloroform, with shaking of the two phases briskly for about 30 s each time. The combined chloroform extracts are shaken with 5 ml of 1 : 30 ammonia. (The ammonia wash is repeated if much copper or cobalt is present.) The ammonia washings are equilibrated with 2 ml of chloroform and added to the main chloroform extract. The nickel is returned to the aqueous phase by shaking the chloroform extract vigorously for 1 min with two 5-ml portions of 0.5 *M* hydrochloric acid. The hydrochloric acid solutions are transferred to a 25-ml volumetric flask and diluted to about 20 ml. Then 1 ml of bromine water is added, followed by 2 ml of concentrated ammonia. The solution is cooled to below 30 C, if necessary.

and 1 ml of dimethylglyoxime solution is added. The mixture is diluted to volume, and the absorbance at 445 nm is measured after 5 min; absorbance due to the solvent is deducted.

The nickel solutions for establishment of the standard curve should be comparable in acidity with the sample solution. The procedure has a nickel sensitivity of 0.0042 $\mu g/cm^2$.

Polarography

West and Dean[709] report a polarographic method for the determination of nickel that is simple, rapid, reliable, sensitive, and free from critical interference from iron and any other substances that are significant in pollution studies. The method is based on the use of sodium fluoride as the supporting electrolyte; this not only produces a well-defined step for nickel, but also acts as a complexing agent to eliminate possible interferences from common metals like iron, cobalt, and copper. The method is well suited for determining nickel in air and water. Particulate nickel samples on fiberglass or membrane filters may be subjected to treatment with nitric and hydrochloric acids to extract nickel from the sample. The pH should be adjusted to 5 ± 1. This pH range also helps to control interferences from other metal ions. Cobalt and iron form very stable fluoride complexes and thus do not interfere.

A suitable portion of the sample solution is pipetted into a 50-ml standard flask; 25 ml of 1 *M* sodium fluoride solution and 1 ml of 0.2% freshly prepared gelatin are added; and the contents are made up to volume and mixed. The solution is filtered through a medium-texture filter paper; the first 10-ml portion of the filtrate is discarded, and a suitable portion is transferred to the electrolytic cell. Nitrogen is bubbled through the solution to remove dissolved oxygen, and the polarogram is recorded. Evaluation of the nickel wave can be made from a standard curve of step height versus concentrations, or a known weight of standard nickel solution can be added to a second aliquot of the sample and the above procedure repeated. The nickel concentration in the sample can be calculated from the measured increase in step height resulting from the known weight of added nickel.

Ring-Oven Methods

The ring oven is a versatile instrument that can be used for the identification and determination of airborne particles (available as the "Trace Oven" from Arthur H. Thomas and Company). The technique offers great promise for field studies, because ring-oven methods are rapid, convenient, sensitive, and reliable. The equipment is inexpensive, and the necessary technique can be acquired with a few hours of practice. The air samples preferably should be collected by means of a sequential tape sampler (such as that of the Gelman Instrument Company, Ann Arbor, Michigan), which gives a sample spot about 13 mm in diameter. Any spot less than 22 mm in diameter can be analyzed directly on the ring oven, thus avoiding any tedious sample-preparation step.

The dust spot from air sampling is centered on the surface of the ring oven, and nickel is determined by the recommended[708] procedure, which is as follows:

1. Add 15 μl of 15% ammonium acetate solution to the spot and wash the nickel particles to the ring zone with water. This deposits nickel in a sharp ring at the ring zone.
2. Add 15 μl of 15% ammonium acetate and 15 μl of 0.5% potassium cyanide and wash to the ring zone with water.
3. Expose the ring zone to formaldehyde fumes for 2 min.
4. Spray 1% ethanolic dimethylglyoxime solution. Wait for 1 min to allow ethyl alcohol to evaporate and expose the ring to ammonia. A brilliant red ring is formed.
5. Compare the intensity of the ring with standard rings and determine the nickel content visually.

The lower limit of identification is 0.08 μg, and the range of determination is 0.1–1.0 μg of nickel. There are no potential interferences. When the ring zone is exposed to formaldehyde, the tetracyanonickelate complex (which is formed during the preliminary treatment of the sample spot with potassium cyanide) is destroyed to form cyanohydrin; this releases the nickel, which then reacts readily with dimethylglyoxime.

NICKEL IN WATER

Most of the analytic methods discussed above can be applied to the determination of nickel in water with slight modifications. The concentration of pollutant in water is generally in the range of parts per billion or parts per trillion. Therefore, unless a preconcentration step is incorporated, most of the analytic methods will fail to work for nickel. A concentration step using a mixed ligand is recommended.[508] The final determination of nickel can then be carried out with any of the analytic methods discussed.

NICKEL CARBONYL AND ITS DETERMINATION

A particular problem exists in the case of the highly toxic nickel carbonyl. Because it is a gas at ordinary temperatures, this substance requires special methods for sampling and analysis. Gases can be sampled by passing them through a hot (60 C) furnace. At 60 C, nickel carbonyl decomposes into carbon monoxide and nickel; the latter can then be collected as particles.[3] Samples can also be passed through a special trapping solution of absolute ethyl alcohol kept at −78 C.[268] Brief *et al.*[60] described five excellent methods for the determination of nickel carbonyl, and the American Industrial Hygiene Association[5] mentions the availability of a field instrument for continuous monitoring with sensitivity down to 10 ppb.

Sunderman *et al.*[618] have developed a very sensitive and rapid method for the determination of nickel carbonyl that uses a gas-chromatographic technique and have measured this compound in blood and breath. The method is dealt with in detail here, because it can serve as a practical method for regular monitoring of industrial atmospheres and thus for diagnosing nickel carbonyl poisoning among industrial workers.

The general sampling procedure consists of trapping air that contains traces of nickel carbonyl in absolute ethyl alcohol at −78 C.[619] For liquid samples, such as blood, 4 ml of the sample is placed in a 25-ml sidearm flask, which is connected to a vacuum pump via an extraction tube containing 10 ml of absolute ethyl alcohol and kept at −78 C by immersion into a Dewar flask that contains a mixture of solidified carbon dioxide and acetone. Nickel carbonyl is extracted from the sample by vacuum and trapped in cold ethyl alcohol. The sample should be kept at −78 C until ready for injection into a chromatographic column.

The instrument assembly consists of a gas chromatograph using an electron-capture detector (with a 200-μc tritium source), the injection port, and the chromatographic column (all kept at 25 C). The liquid phase to be used for the chromatographic fractionations may be Carbowax 20 *M*, Silicone DC-560, Epon 1001, or neopentylglycolsuccinate. Pyrex chromatographic columns 6 ft long and 1/4 in. in inside diameter are packed with a mixture consisting of 5 g of the chosen liquid phase in 100 g of acid-washed 60–80 mesh Chromosorb w. A 1-μl ethanolic sample solution is injected into the chromatographic column by microsyringe. The sensitivity-control knobs of the instrument are adjusted as required. A mixture of argon and methane (95 : 5% vol.) at a flow rate of 60 ml/min is used as the carrier gas.

The criterion for reliable identification of nickel carbonyl in samples is the presence of chromatographic peaks with characteristic retention times and mobility ratios on each of the four chromatographic columns (Table B-2). The most distinct and symmetrical peaks for nickel carbonyl have been obtained by using Carbowax 20 *M*, and it is therefore recommended for quantitative determinations. The relation of peak height to nickel carbonyl concentration is linear throughout the range of measurements. A typical calibration curve constructed by plotting peak heights versus microliters of nickel carbonyl per 10 ml of ethyl alcohol was linear over a range of 0.0125–0.1 μl.

Atomic-Absorption Spectroscopy

Kneip *et al.*[308] have recently proposed a procedure for analysis of nickel in atmospheric particles. Samples are collected by drawing a known volume of air through a membrane or glass fiber filter. The filter samples are ashed and extracted with acid, and the analysis is by atomic-absorption spectroscopy, using the 232.0-nm nickel line. The method is applicable to the determination of nickel in quantities of 0.1–20.0 μg of nickel per milliliter of solution. An atmospheric concentration of 0.005 $\mu g/m^3$ can be detected. For this concentration, a minimal air sample volume of 2,000 m^3 is recommended.

Silica extracted from the glass fiber filter and from the collected particulate matter can cause a significant interference with the measurement of nickel. This interference can be overcome by allowing the acid extracts to stand overnight and centrifuging at about 2,000 rpm for 30 min. If large amounts of antimony or beryllium are suspected, their possible spectroscopic interference should be investigated. Usually, ambient amounts of these elements are not appreciable, and the effects on the analyses can be considered negligible.

The precision of the method has not been reported for air samples; however, in the determination of nickel by a nearly identical method, an average standard deviation of 13% was obtained at normal urban con-

TABLE B-2 Gas-Chromatographic Detection of Nickel Carbonyl in Ethyl Alcohol

Liquid Phase	Retention Time, s Nickel Carbonyl	 Ethyl Alcohol	Ratio of Retention Times, Nickel Carbonyl : Ethyl Alcohol
Epon 1001	19	51	0.37 : 1
Neopentylglycolsuccinate	24	54	0.44 : 1
Carbowax 20 *M*	37	72	0.51 : 1
Silicone DC-560	120	174	0.69 : 1

centrations. The recovery by this method is 88%, provided the matrix of the sample is not appreciably different from that of the standards. Interferences due to the presence of other metals can reduce the accuracy of the method.

An 8 × 10-in. glass fiber filter, of which a 7 × 9-in. section is exposed on the high-volume sampler, is divided into sections. The amount of a filter used depends on the type of sample being prepared–urban or nonurban and individual or composite. The strips for metal analysis are ashed at low temperature (50–250 C). The ashed filter is placed in a glass thimble, which is then placed in an extraction tube. A 125-ml flask is charged with 8 ml of constant boiling (about 19%) hydrochloric acid and 32 ml of 40% nitric acid. The flask is attached to the extraction tube, and the extraction tube is fitted with an Alihn condenser. The acid is refluxed over the sample for 3 h. The sample and extraction thimble remain at the temperature of the boiling acid throughout the extraction.

The extraction tube and condenser are removed from the flask, and the flask is fitted with a thermometer adapter, which serves as a spray retainer. The extracted liquid is concentrated to 1–2 ml on a hot plate and allowed to cool and stand overnight. The concentrated material is quantitatively transferred to a graduated 15-ml centrifuge tube with three washings of 5–10 drops of 1 : 10 hydrochloric acid. The samples are then diluted and centrifuged at 2,000 rpm for 30 min. The supernatant liquid is decanted into polypropylene tubes that are then capped and stored until analysis. One milliliter from each solution is diluted with 1 : 10 hydrochloric acid to 10 ml for atomic-absorption analysis.

For analysis, the instrument is set to the operating conditions recommended by the manufacturer. The instrument should be set to the wavelength of maximal intensity for the 232.0-nm line from the hollow cathode lamp. Standards are prepared fresh daily. The samples are aspirated directly into the instrument, and the absorbance is recorded for comparison with the standards.

NICKEL IN BIOLOGIC MATERIALS

The analytic chemistry of nickel has recently been comprehensively reviewed by Lewis and Ott.[341] Few of the methods for nickel analysis that are discussed by Lewis and Ott are sufficiently sensitive to permit quantitative determinations of nickel in biologic materials. The molar absorptivities of various color reagents that are used for spectrophotometric determinations of nickel are listed in Table B-3. The most sensitive of

TABLE B-3 Color Reagents for Spectrophotometric Determination of Nickel[a]

Reagent	Wavelength, nm	Molar Absorptivity
Dimethylglyoxime in chloroform	375 325	3.5×10^3 5.0×10^3
Benzildioxime in chloroform	406	1.1×10^4
Alpha-furildioxime in chloroform	435	1.6×10^4
Thiotrifluoroacetylacetone in chloroform	256	3.4×10^4
Diethyldithiocarbamate in isoamyl alcohol	325	3.7×10^4

[a] Data from Sunderman,[606] Barratt *et al.*,[30] and Bodart.[52]

these reagents is diethyldithiocarbamate. Sunderman[606] has reported a spectrophotometric method for analysis of nickel in serum and other biologic materials, in which the samples are subjected to acid digestion, and nickel is separated from interfering elements by chloroform extraction of nickel dimethylglyoximate at alkaline pH. Nickel is converted to the diethyldithiocarbamate complex and extracted into isoamyl alcohol. The absorbance of nickel-bisdiethyldithiocarbamate is measured at 325 nm.

Mealor and Townshend[394] have described a kinetic method for determination of nickel that is based on nickel catalysis of formate reduction of permanganate ion to manganate ion at alkaline pH. This reaction can be followed spectrophotometrically at 505 nm (disappearance of permanganate) or at 600 nm (appearance of manganate). This catalytic technique may provide greater sensitivity than the colorimetric reagents listed in Table B-3. However, this method has not yet been applied to measurements of nickel in biologic substances. Pulse polarography,[2, 45, 194] atomic fluorescence,[11, 381], and gas chromatography[31, 42] are also potentially valuable for quantitation of traces of nickel, but these procedures have not yet been applied to analyses of biologic materials.

For practical purposes, atomic-absorption spectrometry is the method currently used for routine analyses of nickel in body fluids and tissues. The various reported atomic-absorption techniques are summarized in Table B-4. An adaptation of the method of Nomoto and Sunderman[440] has recently been selected as a reference procedure for nickel analysis in biologic materials[601] and is described hereafter. This method has also been adapted for atomic-absorption spectrometry with a nonflame atomizer (graphite-tube furnace).[596]

TABLE B-4 Atomic-Absorption Spectrometry of Nickel in Biologic Samples

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Instrument characteristics
  Wavelength: 232.00 nm
  Flame: acetylene–air or acetylene–oxygen; oxidizing (fuel-poor)
  Detection limit: 2–5 μg/liter
Sample preparation (B, blood; P, plasma; S, serum; U, urine; F, feces; H, hair)
  Acid digestion, dimethylglyoxime–chloroform extraction, hydrochloric acid back-extraction (U)[600]
  Acid digestion, ammonium pyrrolidine dithiocarbamate–methylisobutylketone extraction (B,U,F,H)[254,431,449,596]
  Acid digestion (B,P)[250]
  Trichloroacetic acid deproteinization, ammonium pyrrolidine dithiocarbamate–methylisobutylketone extraction (P,S,U)[449,521]
  Direct sampling (50 μl) into graphite furnace[471,613]
Interferences and Precautions
  Special care is essential to minimize contamination and background absorbance
  Adjacent nonabsorbing nickel line (231.98 nm) cannot be resolved
  Inorganic salts are a troublesome cause of nonspecificity

Apparatus

1. Glass syringes fitted with platinum–ruthenium needles or Vacutainer tubes, leadfree, with unsoldered steel needles.
2. Centrifuge tubes, 50 ml.
3. Mechanical shaker.
4. Centrifuge.
5. Mixer (Vortex).
6. pH meter.
7. Pasteur pipettes.
8. Spectrometer, atomic-absorption (Perkin-Elmer model 403) fitted with a nickel hollow-cathode lamp, a Boling three-slot acetylene–air burner, and a 10-in. strip-chart recorder.

Operating Conditions

Gas flow rates: acetylene, 4.2 liters/min; air, 23 liters/min. Wavelength: 232 nm. Nickel-lamp current: 16 mA. Range: UV. Filter settings: out. Entrance slit position: 3. Recorder response position: 2. Recorder setting: 0.25 A, full-scale. Concentration dial setting: 75. Curvature correction: 0.

Reagents

All concentrated acid and base reagents are ultrapure grade. All water is deionized and then distilled in an all-glass still.

1. Nickel stock solution, 50 μg/ml. Place 50 mg of powdered nickel in a 50-ml beaker and dissolve it in a mixture containing 5.0 ml of concentrated nitric acid and 5.0 ml of water, applying heat. Transfer the solution quantitatively to a 1-liter volumetric flask and dilute it to the calibration mark with water.

2. Nickel reference solutions, 0.025 μg/ml, 0.05 μg/ml. Transfer 1.0-ml portions of the nickel stock solution to 2-liter and 1-liter volumetric flasks and dilute to the calibration marks with water.

3. Trichloroacetic acid (TCA), 15 g/100 ml. Dissolve 150 g of metal-free TCA in 1 liter of water. Store the solution at 4 C. Prepare fresh every 2 wk.

4. Hydrochloric acid, 1 N. Dilute 8.0 ml of concentrated (36%) hydrochloric acid to 100 ml with water.

5. Phthalate buffer solution, pH 2.5. In a 1-liter volumetric flask dissolve 10.2 g of potassium hydrogen phthalate in 39 ml of 1 N hydrochloric acid added to approximately 400 ml of water. Dilute to the calibration mark with water. Transfer the contents to a 2-liter separatory funnel. Test the pH of the solution with a pH meter and adjust it, if necessary, to 2.5 by addition of either potassium hydrogen phthalate or hydrochloric acid.

6. Sulfuric acid–nitric acid mixture, 1 : 5. Mix 1 volume of concentrated (96%) sulfuric acid with 5 volumes of concentrated (65%) nitric acid.

7. Perchloric acid, concentrated (70%).

8. Hydrochloric acid, 1.2 N. Dilute 10.0 ml of concentrated hydrochloric acid to 100 ml with water.

9. Methylisobutylketone (MIBK).

10. Ammonium hydroxide, concentrated (25%).

11. Ammonium hydroxide, 1.5 N. Dilute 10.0 ml of concentrated ammonium hydroxide to 100 ml with water.

12. Ammonium pyrrolidine dithiocarbamate (APDC), 2 g/100 ml. Dissolve 1 g of APDC in 50 ml of water. Extract the solution twice, using 5.0 ml of MIBK each time. Prepare fresh each day.

13. MIBK saturated with TCA. Place 400 ml of MIBK and 100 ml of TCA solution into a 1-liter separatory funnel. Shake the mixture and allow it to stand for 1 h at 4 C. Remove the MIBK phase, and then centrifuge it to eliminate all traces of the aqueous phase. Prepare fresh each week. This solution is used to establish the spectrometer baseline.

14. MIBK–APDC solution. Place 10.0 ml of the TCA solution in a 50-ml centrifuge tube. Adjust the pH of the solution to 2.5 by dropwise addition of concentrated (25%) ammonium hydroxide. Add 5.0 ml of the APDC solution and 30 ml of MIBK. Mix the contents of the tube

with a Vortex mixer, and then cool the tube in an ice bath. Centrifuge the tube for 15 min at 900 g. Remove the MIBK phase. Store the solution in a refrigerator for up to 1 wk. This solution is used daily to remove traces of nickel from the burner system.

Sample Preparation

SERUM

1. Transfer duplicate 5.0-ml serum samples to 50-ml centrifuge tubes. Into additional duplicate sets of 50-ml centrifuge tubes place 1.0 ml of each nickel reference solution and 4.0 ml of water. These reference samples are equivalent to 0.5 μg and 1.0 μg of nickel per 100 ml of serum. Place duplicate 5.0-ml water samples in 50-ml tubes to serve as the reagent blanks.
2. Constantly mixing, add 6.0 ml of TCA solution slowly to each tube.
3. Agitate the tubes for 30 min in a mechanical shaker, and then centrifuge them for 15 min at 900 g.
4. Decant the proteinfree supernatant phases into clean 50-ml centrifuge tubes. Add 4.0 ml of TCA solution to each of the original tubes.
5. Resuspend the precipitated proteins with a Vortex mixer, and then recentrifuge the suspensions for 15 min at 900 g.
6. Combine the proteinfree washings with the corresponding original supernatant fluids, add 2.0 ml of the phthalate buffer to each combined proteinfree extract, and then proceed with analysis.

URINE, WHOLE BLOOD, HAIR, AND OTHER TISSUES

1. Transfer the specimen (i.e., 50 ml of urine, 10.0 ml of heparinized whole blood, 2.0 g of feces, 1.0 g of hair, or 10.0 ml of a 20% tissue homogenate) to one of a pair of 125-ml Erlenmeyer flasks. Add 10.0 ml of the sulfuric acid–nitric acid mixture to each flask. Process corresponding samples of each reference solution and of water for reagent blanks in the same manner as the specimen.
2. Heat the flasks gently on a hot plate, intermittently swirling, until the contents are clear; then continue the digestion with increased heat until charring occurs and white fumes of sulfur trioxide are generated. Allow the flasks to cool.
3. Add 2.0 ml of the sulfuric acid–nitric acid mixture and 0.5 ml of concentrated perchloric acid, and then continue the digestion for 20 min after the samples have become practically colorless.

4. Add 1.0 ml of the sulfuric acid–nitric acid mixture and 0.25 ml of concentrated perchloric acid, and then continue the digestion for 20 min after the samples have become practically colorless. The final volume of the digestion mixture should be less than 2.0 ml.

5. When using a urine specimen, cool the flasks and transfer their contents quantitatively with four washes of water to 50-ml centrifuge tubes. Adjust the volumes to approximately 20 ml by addition of water. When using whole blood, feces, or homogenates of tissues (such as muscle or liver) that contain appreciable amounts of iron, cool the flasks and add 5.0 ml of 1.2 N hydrochloric acid. Heat the flasks to boiling, and then allow the contents to cool. Add 6.0 ml of MIBK and shake the flasks to extract the iron. After the phases have separated, aspirate and discard the MIBK layer. Transfer the residual aqueous phases quantitatively with four washes of water to 50-ml centrifuge tubes. Adjust the volumes to approximately 15 ml by addition of water, and then centrifuge the tubes for 5 min at 900 *g*. Aspirate and discard any remaining traces of MIBK.

6. Add 2.0 ml of the phthalate buffer, and then proceed with analysis.

Analysis

1. Add concentrated ammonium hydroxide dropwise to each sample, constantly mixing, until the pH reaches approximately 2.0. Monitor this with a pH meter. Gradually adjust the pH to 2.5 (2.4–2.6) by dropwise addition of 1.5 N ammonium hydroxide.
2. Add 2.0 ml of the APDC solution to each sample and mix.
3. Add 2.0 ml of MIBK and mix for 20 s with a Vortex mixer.
4. Place the sample containers in an ice bath for 10 min, and then centrifuge them for 10 min at 900 *g*.
5. Using Pasteur pipettes, transfer each MIBK extract to a small stoppered test tube, exercising care to avoid transfer of the aqueous phase.
6. Aspirate MIBK reagent into the burner of the atomic-absorption spectrometer. Adjust the flame to dark blue, with a bright-blue segment (5 mm high) immediately above the burner. Allow the MIBK to aspirate for 20–30 min to stabilize the flame conditions. Verify the absolute stability of the recorder baseline by aspirating MIBK saturated with TCA for 20 min, while the strip-chart recorder is operating. Finally, aspirate the MIBK–APDC solution for 1 min to remove any residue of nickel from the burner system. The spectrometer is now ready for analysis.
7. Aspirate the MIBK extracts into the burner and record the absorbances of all samples.

8. Measure the heights of the absorbance peaks.
9. Determine the nickel concentration in the specimen by comparing the heights of the absorbance peaks of its extracts with those of the reference samples.

Accuracy and Precision

As a measure of the day-to-day variability of this method, the coefficient of variation for 17 consecutive daily measurements of nickel concentration in a pooled specimen of serum was 9.9%. As measures of within-run variability, the coefficient of variation for duplicate analyses of nickel in 91 serum samples was 8.7%, and the coefficient of variation for duplicate analyses of nickel in 32 specimens of whole blood was 11.3%. The coefficient of variation for duplicate analyses of nickel in 50 urine specimens was 10.3%. The recovery of nickel added to serum, blood, urine, and tissues in a concentration of 2.5 μg/100 ml or 2.5 μg/100 g (wet weight) averaged 101%, 102%, 100%, and 98% respectively.[449]

Interfering Substances

Cadmium and gold salts can cause slight inhibition in the atomic absorption of nickel, owing to the absorption of nickel on insoluble complexes of cadmium and gold with pyrrolidine dithiocarbamate. Such interference would be detectable only when the concentrations of cadmium and gold exceeded 10 and 25 μg/100 ml, respectively.[449]

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